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                  present
 NEWS  4  AUG 05  New pricing for EUROPATFULL and PCTFULL effective
                  August 1, 2003
 NEWS  5  AUG 13  Field Availability (/FA) field enhanced in BEILSTEIN
 NEWS  6  AUG 18  Data available for download as a PDF in RDISCLOSURE
 NEWS  7  AUG 18  Simultaneous left and right truncation added to PASCAL
 NEWS  8  AUG 18  FROSTI and KOSMET enhanced with Simultaneous Left and Righ
                  Truncation
 NEWS  9  AUG 18  Simultaneous left and right truncation added to ANABSTR
 NEWS 10  SEP 22  DIPPR file reloaded
 NEWS 11  SEP 25  INPADOC: Legal Status data to be reloaded
 NEWS 12  SEP 29  DISSABS now available on STN
 NEWS 13  OCT 10  PCTFULL: Two new display fields added
 NEWS 14  OCT 21  BIOSIS file reloaded and enhanced
 NEWS 15  OCT 28  BIOSIS file segment of TOXCENTER reloaded and enhanced

 NEWS EXPRESS  NOVEMBER 14 CURRENT WINDOWS VERSION IS V6.01c, CURRENT
               MACINTOSH VERSION IS V6.0b(ENG) AND V6.0Jb(JP),
               AND CURRENT DISCOVER FILE IS DATED 23 SEPTEMBER 2003
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FILE 'HOME' ENTERED AT 12:49:06 ON 21 NOV 2003

=> file medline, uspatful, wpids, jicst, fsta, hcaplus
COST IN U.S. DOLLARS                          SINCE FILE      TOTAL
                                                 ENTRY    SESSION
FULL ESTIMATED COST                               1.68       1.68

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FILE 'USPATFULL' ENTERED AT 12:53:40 ON 21 NOV 2003
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FILE 'WPIDS' ENTERED AT 12:53:40 ON 21 NOV 2003
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=> s IgE fragment
L1          898 IGE FRAGMENT

=> s IgE
L2        59183 IGE

=> s clostridium botulinum
L3         8710 CLOSTRIDIUM BOTULINUM

=>  s neisseria gonorrheae
L4          406 NEISSERIA GONORRHEAE

=> s fusion protein or hybrid protein
L5        73853 FUSION PROTEIN OR HYBRID PROTEIN

=> s mastocytes
L6          719 MASTOCYTES

=> s basophils
L7        14279 BASOPHILS

=> s tetanus toxin
L8         6169 TETANUS TOXIN

=> s l2 and l5
L9         5949 L2 AND L5

=> s l9 and l6
L10           5 L9 AND L6

=> d l10 ti abs ibib tot

L10  ANSWER 1 OF 5  USPATFULL on STN
TI     Cloning and sequencing of the allergen Dac g5 of Dactylis glomerata
       pollen, its preparation and its use
AB     A purified nucleic acid molecule comprising a nucleotide sequence coding
       for allergen Dac g5 havinge amino acid sequence SEQ ID NO. 2, a
       derivative or a fragment thereof.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
ACCESSION NUMBER:        2003:213243  USPATFULL
TITLE:                   Cloning and sequencing of the allergen Dac g5 of
                         Dactylis glomerata pollen, its preparation and its use
INVENTOR(S):             Van Ree, Ronald, Amsterdam, NETHERLANDS
                         Van Oort, Erica, Vleuten, NETHERLANDS
                         Bonneau, Caroline, Rouen, FRANCE
                         Faye, Loic, Saint-Jacques-sur-Darnetal, FRANCE
```

	Gomord, Veronique, Rouen, FRANCE
PATENT ASSIGNEE(S):	Seita Groupe Altadis, Paris Cedex, FRANCE (non-U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2003147880	A1	20030807
APPLICATION INFO.:	US 2002-303426	A1	20021125 (10)

RELATED APPLN. INFO.: Continuation of Ser. No. WO 2001-FR1666, filed on 29 May 2001, UNKNOWN

	NUMBER	DATE
PRIORITY INFORMATION:	FR 2000-6857	20000529

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: SCHNADER HARRISON SEGAL & LEWIS, LLP, 1600 MARKET STREET, SUITE 3600, PHILADELPHIA, PA, 19103
NUMBER OF CLAIMS: 20
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 2 Drawing Page(s)
LINE COUNT: 829
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L10 ANSWER 2 OF 5 USPATFULL on STN
TI Factors participating in degranulation of mast cells, dnas encoding the same, method of screening of these factors and the inhibitors
AB The present invention provides a novel protein that regulates degranulation of mast cells (degranulation regulator), a gene encoding it, a protein (conjugate factor) that interacts with the regulator, a gene encoding it, a screening method of an inhibitor of the degranulation, which uses this degranulation regulator and the conjugate factor, an inhibitor obtained by the screening method and the like.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
ACCESSION NUMBER: 2003:207275 USPATFULL
TITLE: Factors participating in degranulation of mast cells, dnas encoding the same, method of screening of these factors and the inhibitors
INVENTOR(S): Yamada, Tsuyoshi, Chiba, JAPAN
Ido, Motoharu, Shiga, JAPAN

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 2003143633	A1	20030731	
APPLICATION INFO.:	US 2002-258107	A1	20021219	(10)
	WO 2001-JP3268		20010416	

	NUMBER	DATE
PRIORITY INFORMATION:	JP 2000-118408	20000419

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: LEYDIG VOIT & MAYER, LTD, TWO PRUDENTIAL PLAZA, SUITE 4900, 180 NORTH STETSON AVENUE, CHICAGO, IL, 60601-6780
NUMBER OF CLAIMS: 41
EXEMPLARY CLAIM: 1
LINE COUNT: 2008
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L10 ANSWER 3 OF 5 USPATFULL on STN
TI **Hybrid protein** for inhibiting the degranulation of **mastocytes** and the use thereof
AB A **hybrid protein** contains a protein that binds to a

receptor of **mastocytes** and basophils and is endocyted by them. The protein can be **IgE**; **IgE** fragment; **IgE** Fc fragment; antibody against **IgE** receptor of **mastocytes** and basophils; fragment of the antibody against the **IgE** receptor of **mastocytes** and basophils; antibody against mastocyte specific potassium channel; and mast cell degranulating peptide. The **hybrid protein** also contains a protease cleaving proteins of the secretion process of the **mastocytes** and basophils so as to inhibit the secretion process without killing the **mastocytes** and basophils. The protease can be light chain Clostridium botulinum toxin; proteolytically active fragment of the light chain of a Clostridium botulinum toxin containing an amino acid sequence His-Xaa-Xaa-Xaa-His-Xaa-Xaa-His wherein Xaa is an amino acid; light chain of the tetanus toxin; proteolytically active fragment of the light chain of the tetanus toxin containing His-Asp-Leu-Ile-His-Val-Leu-His; IgA protease of Neisseria gonorrhoeae; and proteolytic domain of the IgA protease of Neisseria gonorrhoeae.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

ACCESSION NUMBER:	2003:86306 USPATFULL
TITLE:	**Hybrid protein** for inhibiting the degranulation of **mastocytes** and the use thereof
INVENTOR(S):	Bigalke, Hans, Hannover, GERMANY, FEDERAL REPUBLIC OF Frevert, Jurgen, Berlin, GERMANY, FEDERAL REPUBLIC OF
PATENT ASSIGNEE(S):	BioteCon Gesellschaft fur biotechnologische Entwicklung und consulting mbH, Berlin, DE, 10589 (non-U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2003059912	A1	20030327
APPLICATION INFO.:	US 2002-64903	A1	20020827 (10)
RELATED APPLN. INFO.:	Continuation-in-part of Ser. No. US 2001-700540, filed on 19 Jan 2001, PENDING A 371 of International Ser. No. WO 1999-EP3272, filed on 12 May 1999, UNKNOWN		

	NUMBER	DATE
PRIORITY INFORMATION:	DE 1998-19821285	19980513

DOCUMENT TYPE:	Utility
FILE SEGMENT:	APPLICATION
LEGAL REPRESENTATIVE:	GUDRUN E. HUCKETT, LONSSTR. 53, WUPPERTAL, 42289
NUMBER OF CLAIMS:	11
EXEMPLARY CLAIM:	1
LINE COUNT:	576

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L10 ANSWER 4 OF 5 HCAPLUS COPYRIGHT 2003 ACS on STN

TI Inhibiting the degranulation in **mastocytes** using a **hybrid protein** comprising a receptor-binding protein fused to a protease cleaving a protein of the secretion process

AB A **hybrid protein** is provided contg. a protein that binds to a receptor of **mastocytes** and basophils and is endocytosed by them. The protein can be **IgE**, **IgE** fragment, **IgE** Fc fragment, antibody against the **IgE** receptor of **mastocytes** and basophils, a fragment of the antibody against the **IgE** receptor of **mastocytes** and basophils, an antibody against mastocyte-specific potassium channel, or mast cell degranulating peptide. The **hybrid protein** also contains a protease which cleaves proteins of the secretion process of the **mastocytes** and basophils so as to inhibit the secretion process without killing the **mastocytes** and basophils. The protease can be the light chain of Clostridium botulinum toxin or its proteolytic

fragments contg. a His-Xaa-Xaa-Xaa-His-Xaa-Xaa-His sequence, the light chain of the tetanus toxin or proteolytically active fragment of the light chain contg. His-Asp-Leu-Ile-His-Val-Leu-His, or an IgA protease of Neisseria gonorrhoeae and its proteolytic domain. Thus, a **hybrid protein** comprising **IgE** fused to the light chain of either Clostridium botulinum toxin or tetanus toxin prevents allergic shock caused by dying **mastocytes**.

ACCESSION NUMBER: 2003:241912 HCAPLUS
DOCUMENT NUMBER: 138:265639
TITLE: Inhibiting the degranulation in **mastocytes** using a **hybrid protein** comprising a receptor-binding protein fused to a protease cleaving a protein of the secretion process
INVENTOR(S): Bigalke, Hans; Frevert, Jurgen
PATENT ASSIGNEE(S): Biotecon Gesellschaft Fur Biotechnologische Entwicklung Und Consulting Mbh, Germany
SOURCE: U.S. Pat. Appl. Publ., 7 pp., Cont.-in-part of U.S. Ser. No. 700,540.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2003059912	A1	20030327	US 2002-64903	20020827
WO 9958571	A2	19991118	WO 1999-EP3272	19990512
WO 9958571	A3	20000203		

W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: DE 1998-19821285 A 19980513
WO 1999-EP3272 W 19990512
US 2001-700540 A2 20010119

L10 ANSWER 5 OF 5 HCAPLUS COPYRIGHT 2003 ACS on STN
TI **Hybrid protein** for inhibiting the degranulation of **mastocytes** and the use thereof
AB The invention relates to a **hybrid protein** comprising or comprised of (i) a known protein which binds to **mastocytes** and/or basophils in a known manner and/or is absorbed thereby, and of (ii) a protease which splits one or more proteins of the secretory app. of the **mastocytes** and/or basophils. The examples discuss the synthesis of these hybrid proteins using expression vectors expressed in E. coli.

ACCESSION NUMBER: 1999:736768 HCAPLUS
DOCUMENT NUMBER: 131:332099
TITLE: **Hybrid protein** for inhibiting the degranulation of **mastocytes** and the use thereof
INVENTOR(S): Bigalke, Hans; Frevert, Jurgen
PATENT ASSIGNEE(S): Biotecon Gesellschaft fur Biotechnologische Entwicklung und Consulting m.b.H, Germany
SOURCE: PCT Int. Appl., 22 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 2

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9958571	A2	19991118	WO 1999-EP3272	19990512
WO 9958571	A3	20000203		
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2331274	AA	19991118	CA 1999-2331274	19990512
AU 9942605	A1	19991129	AU 1999-42605	19990512
AU 755513	B2	20021212		
BR 9910359	A	20010109	BR 1999-10359	19990512
EP 1084146	A2	20010321	EP 1999-950347	19990512
EP 1084146	B1	20021113		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, FI				
JP 2002514659	T2	20020521	JP 2000-548373	19990512
AT 227739	E	20021115	AT 1999-950347	19990512
ES 2187200	T3	20030516	ES 1999-950347	19990512
RU 2214420	C2	20031020	RU 2000-131217	19990512
NO 2000005637	A	20001108	NO 2000-5637	20001108
HK 1036994	A1	20030221	HK 2001-106685	20010921
US 2003059912	A1	20030327	US 2002-64903	20020827
PRIORITY APPLN. INFO.:			DE 1998-19821285 A	19980513
			WO 1999-EP3272 W	19990512
			US 2001-700540 A2	20010119

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     FILE 'MEDLINE, USPATFULL, WPIDS, JICST-EPLUS, FSTA, HCAPLUS' ENTERED AT
     12:53:40 ON 21 NOV 2003
L1           898 S IGE FRAGMENT
L2         59183 S IGE
L3          8710 S CLOSTRIDIUM BOTULINUM
L4           406 S NEISSERIA GONORRHEAE
L5         73853 S FUSION PROTEIN OR HYBRID PROTEIN
L6           719 S MASTOCYTES
L7         14279 S BASOPHILS
L8          6169 S TETANUS TOXIN
L9          5949 S L2 AND L5
L10            5 S L9 AND L6

=> s l3 and type A
   4 FILES SEARCHED...
L11        1541 L3 AND TYPE A

=> s IgA protease
L12         383 IGA PROTEASE

=> s l2 and toxin
L13        4861 L2 AND TOXIN

=> s l13 and transport
L14        1816 L13 AND TRANSPORT
```

=> s l14 and l6
L15 1 L14 AND L6

=> d l15 ti abs ibib tot

L15 ANSWER 1 OF 1 USPATFULL on STN
TI Hybrid protein for inhibiting the degranulation of **mastocytes** and the use thereof
AB A hybrid protein contains a protein that binds to a receptor of **mastocytes** and basophils and is endocyted by them. The protein can be **IgE**; **IgE** fragment; **IgE** Fc fragment; antibody against **IgE** receptor of **mastocytes** and basophils; fragment of the antibody against the **IgE** receptor of **mastocytes** and basophils; antibody against mastocyte specific potassium channel; and mast cell degranulating peptide. The hybrid protein also contains a protease cleaving proteins of the secretion process of the **mastocytes** and basophils so as to inhibit the secretion process without killing the **mastocytes** and basophils. The protease can be light chain Clostridium botulinum **toxin**; proteolytically active fragment of the light chain of a Clostridium botulinum **toxin** containing an amino acid sequence His-Xaa-Xaa-Xaa-His-Xaa-Xaa-His wherein Xaa is an amino acid; light chain of the tetanus **toxin**; proteolytically active fragment of the light chain of the tetanus **toxin** containing His-Asp-Leu-Ile-His-Val-Leu-His; IgA protease of Neisseria gonorrhoeae; and proteolytic domain of the IgA protease of Neisseria gonorrhoeae.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

ACCESSION NUMBER:	2003:86306 USPATFULL
TITLE:	Hybrid protein for inhibiting the degranulation of **mastocytes** and the use thereof
INVENTOR(S):	Bigalke, Hans, Hannover, GERMANY, FEDERAL REPUBLIC OF Frevert, Jurgen, Berlin, GERMANY, FEDERAL REPUBLIC OF
PATENT ASSIGNEE(S):	BioteCon Gesellschaft fur biotechnologische Entwicklung und consulting mbH, Berlin, DE, 10589 (non-U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2003059912	A1	20030327
APPLICATION INFO.:	US 2002-64903	A1	20020827 (10)

RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 2001-700540, filed on 19 Jan 2001, PENDING A 371 of International Ser. No. WO 1999-EP3272, filed on 12 May 1999, UNKNOWN

	NUMBER	DATE
PRIORITY INFORMATION:	DE 1998-19821285	19980513

DOCUMENT TYPE:	Utility
FILE SEGMENT:	APPLICATION
LEGAL REPRESENTATIVE:	GUDRUN E. HUCKETT, LONSSTR. 53, WUPPERTAL, 42289
NUMBER OF CLAIMS:	11
EXEMPLARY CLAIM:	1
LINE COUNT:	576

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

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FILE 'MEDLINE, USPATFULL, WPIDS, JICST-EPLUS, FSTA, HCAPLUS' ENTERED AT 12:53:40 ON 21 NOV 2003
L1 898 S IGE FRAGMENT

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L2        59183 S IGE
L3         8710 S CLOSTRIDIUM BOTULINUM
L4          406 S NEISSERIA GONORRHEAE
L5        73853 S FUSION PROTEIN OR HYBRID PROTEIN
L6          719 S MASTOCYTES
L7        14279 S BASOPHILS
L8         6169 S TETANUS TOXIN
L9         5949 S L2 AND L5
L10           5 S L9 AND L6
L11        1541 S L3 AND TYPE A
L12         383 S IGA PROTEASE
L13        4861 S L2 AND TOXIN
L14        1816 S L13 AND TRANSPORT
L15           1 S L14 AND L6

=> s l14 and l7
L16         406 L14 AND L7

=> s l16 and l1
L17           6 L16 AND L1

=> d l17 ti abs ibib tot

L17  ANSWER 1 OF 6  USPATFULL on STN
TI     Anti-IgE antibodies
AB     The present invention relates to a method for adjusting the affinity of
       a polypeptide to a target molecule by a combination of steps, including:
       (1) the identification of aspartyl residues which are prone to
       isomerization; (2) the substitution of alternative residues and
       screening the resulting mutants for affinity against the target molecule
       In a preferred embodiment, the method of subtituting residues is
       affinity maturation with phage display (AMPD). In a further preferred
       embodiment the polypeptide is an antibody and the target molecule is an
       antigen. In a further preferred embodiment, the antibody is anti-
       IgE and the target molecule is IgE. In another
       embodiment, the invention relates to an anti-IgE antibody
       having improved affinity to IgE.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
ACCESSION NUMBER:        2003:214601  USPATFULL
TITLE:                   Anti-IgE antibodies
INVENTOR(S):             Lowman, Henry B., El Granada, CA, UNITED STATES
                         Presta, Leonard G., San Francisco, CA, UNITED STATES
                         Jardieu, Paula M., San Mateo, CA, UNITED STATES
                         Lowe, John, Daly City, CA, UNITED STATES
PATENT ASSIGNEE(S):      Genentech, Inc. (U.S. corporation)

                              NUMBER        KIND    DATE
                         ---------------- ------ --------
PATENT INFORMATION:      US 2003149244      A1   20030807
APPLICATION INFO.:       US 2002-113996     A1   20020401  (10)
RELATED APPLN. INFO.:    Continuation of Ser. No. US 2001-920171, filed on 1 Aug
                         2001, PENDING Continuation of Ser. No. US 1999-296005,
                         filed on 21 Apr 1999, GRANTED, Pat. No. US 6290957
                         Continuation of Ser. No. US 1997-887352, filed on 2 Jul
                         1997, GRANTED, Pat. No. US 5994511
DOCUMENT TYPE:           Utility
FILE SEGMENT:            APPLICATION
LEGAL REPRESENTATIVE:    GENENTECH, INC., 1 DNA WAY, SOUTH SAN FRANCISCO, CA,
                         94080.
NUMBER OF CLAIMS:        31
EXEMPLARY CLAIM:         1
NUMBER OF DRAWINGS:      19 Drawing Page(s)
LINE COUNT:              5839
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CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L17 ANSWER 2 OF 6 USPATFULL on STN
TI Hybrid protein for inhibiting the degranulation of mastocytes and the use thereof
AB A hybrid protein contains a protein that binds to a receptor of mastocytes and **basophils** and is endocyted by them. The protein can be **IgE**; **IgE fragment**; **IgE** Fc fragment; antibody against **IgE** receptor of mastocytes and **basophils**; fragment of the antibody against the **IgE** receptor of mastocytes and **basophils**; antibody against mastocyte specific potassium channel; and mast cell degranulating peptide. The hybrid protein also contains a protease cleaving proteins of the secretion process of the mastocytes and **basophils** so as to inhibit the secretion process without killing the mastocytes and **basophils**. The protease can be light chain Clostridium botulinum **toxin**; proteolytically active fragment of the light chain of a Clostridium botulinum **toxin** containing an amino acid sequence His-Xaa-Xaa-Xaa-His-Xaa-Xaa-His wherein Xaa is an amino acid; light chain of the tetanus **toxin**; proteolytically active fragment of the light chain of the tetanus **toxin** containing His-Asp-Leu-Ile-His-Val-Leu-His; IgA protease of Neisseria gonorrhoeae; and proteolytic domain of the IgA protease of Neisseria gonorrhoeae.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
ACCESSION NUMBER: 2003:86306 USPATFULL
TITLE: Hybrid protein for inhibiting the degranulation of mastocytes and the use thereof
INVENTOR(S): Bigalke, Hans, Hannover, GERMANY, FEDERAL REPUBLIC OF
Frevert, Jurgen, Berlin, GERMANY, FEDERAL REPUBLIC OF
PATENT ASSIGNEE(S): BioteCon Gesellschaft fur biotechnologische Entwicklung und consulting mbH, Berlin, DE, 10589 (non-U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2003059912	A1	20030327
APPLICATION INFO.:	US 2002-64903	A1	20020827 (10)

RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 2001-700540, filed on 19 Jan 2001, PENDING A 371 of International Ser. No. WO 1999-EP3272, filed on 12 May 1999, UNKNOWN

	NUMBER	DATE
PRIORITY INFORMATION:	DE 1998-19821285	19980513

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: GUDRUN E. HUCKETT, LONSSTR. 53, WUPPERTAL, 42289
NUMBER OF CLAIMS: 11
EXEMPLARY CLAIM: 1
LINE COUNT: 576
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L17 ANSWER 3 OF 6 USPATFULL on STN
TI Anti-**IgE** antibodies
AB The present invention relates to a method for adjusting the affinity of a polypeptide to a target molecule by a combination of steps, including: (1) the identification of aspartyl residues which are prone to isomerization; (2) the substitution of alternative residues and screening the resulting mutants for affinity against the target molecule. In a preferred embodiment, the method of subtituting residues is affinity maturation with phage display (AMPD). In a further preferred embodiment the polypeptide is an antibody and the target molecule is an antigen. In a further preferred embodiment, the antibody is anti-

IgE and the target molecule is **IgE**. In another embodiment, the invention relates to an anti-**IgE** antibody having improved affinity to **IgE**.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

ACCESSION NUMBER:	2002:105676 USPATFULL
TITLE:	Anti-**IgE** antibodies
INVENTOR(S):	Lowman, Henry B., El Granada, CA, UNITED STATES Presta, Leonard G., San Francisco, CA, UNITED STATES Jardieu, Paula M., San Mateo, CA, UNITED STATES Lowe, John, Daly City, CA, UNITED STATES
PATENT ASSIGNEE(S):	Genentech, Inc. (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2002054878	A1	20020509
APPLICATION INFO.:	US 2001-920171	A1	20010801 (9)

RELATED APPLN. INFO.:	Continuation of Ser. No. US 1999-296005, filed on 21 Apr 1999, GRANTED, Pat. No. US 6290957 Continuation of Ser. No. US 1997-887352, filed on 2 Jul 1997, GRANTED, Pat. No. US 5994511
DOCUMENT TYPE:	Utility
FILE SEGMENT:	APPLICATION
LEGAL REPRESENTATIVE:	GENENTECH, INC., 1 DNA WAY, SOUTH SAN FRANCISCO, CA, 94080
NUMBER OF CLAIMS:	31
EXEMPLARY CLAIM:	1
NUMBER OF DRAWINGS:	19 Drawing Page(s)
LINE COUNT:	5846

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L17 ANSWER 4 OF 6 USPATFULL on STN

TI Anti-**IgE** antibodies and method of improving polypeptides

AB The present invention relates to a method for adjusting the affuinity of a polypeptide to a target molecule by a combination of steps, including: (1) the identification of aspartyl residues which are prone to isomerization; (2) the substitution of alternative residues and screening the resulting mutants for affinity against the target molecule. In a preferred embodiment, the method of subtituting residues is affinity maturation with phage display (AMPD). In a further preferred embodiment the polypeptide is an antibody and the target molecule is an antigen. In a further preferred embodiment, the antibody is anti-**IgE** and the target molecule is **IgE**. In another embodiment, the invention relates to an anti-**IgE** antibody having improved affinity to **IgE**.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

ACCESSION NUMBER:	2001:157795 USPATFULL
TITLE:	Anti-**IgE** antibodies and method of improving polypeptides
INVENTOR(S):	Lowman, Henry B., 400 San Juan Ave., El Granada, CA, United States 94018 Presta, Leonard G., 1900 Gough St. #206, San Francisco, CA, United States 94109 Jardieu, Paula M., 33 Hayward Ave. #110, San Mateo, CA, United States 94401-4319 Lowe, John, 396 Michelle La., Daly City, CA, United States 94080

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 6290957	B1	20010918
APPLICATION INFO.:	US 1999-296005		19990421 (9)

RELATED APPLN. INFO.:	Continuation of Ser. No. US 1997-887352, filed on 2 Jul

1997, now patented, Pat. No: US 5994511
DOCUMENT TYPE: Utility
FILE SEGMENT: GRANTED
PRIMARY EXAMINER: Saunders, David
LEGAL REPRESENTATIVE: Svoboda, Craig G.
NUMBER OF CLAIMS: 19
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 21 Drawing Figure(s); 19 Drawing Page(s)
LINE COUNT: 4910
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L17 ANSWER 5 OF 6 USPATFULL on STN
TI Anti-**IgE** antibodies and method of improving polypeptides
AB The present invention relates to a method for adjusting the affinity of a polypeptide to a target molecule by a combination of steps, including: (1) the identification of aspartyl residues which are prone to isomerization; (2) the substitution of alternative residues and screening the resulting mutants for affinity against the target molecule. In a preferred embodiment, the method of substituting residues is affinity maturation with phage display (AMPD). In a further preferred embodiment the polypeptide is an antibody and the target molecule is an antigen. In a further preferred embodiment, the antibody is anti-**IgE** and the target molecule is **IgE**. In another embodiment, the invention relates to an anti-**IgE** antibody having improved affinity to **IgE**.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
ACCESSION NUMBER: 2001:4887 USPATFULL
TITLE: Anti-**IgE** antibodies and method of improving polypeptides
INVENTOR(S): Lowman, Henry B., El Granada, CA, United States
Presta, Leonard G., San Francisco, CA, United States
Jardieu, Paula M., San Mateo, CA, United States
Lowe, John, Daly City, CA, United States
PATENT ASSIGNEE(S): Genentech, Inc., South San Francisco, CA, United States (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 6172213	B1	20010109	
APPLICATION INFO.:	US 1998-109207		19980630	(9)

	NUMBER	DATE	
PRIORITY INFORMATION:	US 1997-51554P	19970702	(60)

DOCUMENT TYPE: Patent
FILE SEGMENT: Granted
PRIMARY EXAMINER: Chan, Christina Y.
ASSISTANT EXAMINER: Ewoldt, Gerald R.
LEGAL REPRESENTATIVE: Svoboda, Craig G.
NUMBER OF CLAIMS: 9
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 23 Drawing Figure(s); 19 Drawing Page(s)
LINE COUNT: 4829
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L17 ANSWER 6 OF 6 USPATFULL on STN
TI Anti-**IgE** antibodies and methods of improving polypeptides
AB The present invention relates to a method for adjusting the affinity of a polypeptide to a target molecule by a combination of steps, including: (1) the identification of aspartyl residues which are prone to isomerization; (2) the substitution of alternative residues and screening the resulting mutants for affinity against the target molecule. In a preferred embodiment, the method of subtituting residues

is affinity maturation with phage display (AMPD). In a further preferred embodiment the polypeptide is an antibody and the target molecule is an antigen. In a further preferred embodiment, the antibody is anti-**IgE** and the target molecule is **IgE**. In another embodiment, the invention relates to an anti-**IgE** antibody having improved affinity to **IgE**.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

ACCESSION NUMBER:	1999:155894 USPATFULL
TITLE:	Anti-**IgE** antibodies and methods of improving polypeptides
INVENTOR(S):	Lowman, Henry B., El Granada, CA, United States Presta, Leonard G., San Francisco, CA, United States Jardieu, Paula M., San Mateo, CA, United States Lowe, John, Daly City, CA, United States
PATENT ASSIGNEE(S):	Genentech, Inc., South San Francisco, CA, United States (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 5994511		19991130	
APPLICATION INFO.:	US 1997-887352		19970702	(8)

DOCUMENT TYPE:	Utility
FILE SEGMENT:	Granted
PRIMARY EXAMINER:	Saunders, David
LEGAL REPRESENTATIVE:	Svoboda, Craig G.
NUMBER OF CLAIMS:	11
EXEMPLARY CLAIM:	1
NUMBER OF DRAWINGS:	21 Drawing Figure(s); 19 Drawing Page(s)
LINE COUNT:	5816

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

```
=> s degranulation
L18      15947 DEGRANULATION

=> d his

     (FILE 'HOME' ENTERED AT 12:49:06 ON 21 NOV 2003)

     FILE 'MEDLINE, USPATFULL, WPIDS, JICST-EPLUS, FSTA, HCAPLUS' ENTERED AT
     12:53:40 ON 21 NOV 2003
L1         898 S IGE FRAGMENT
L2       59183 S IGE
L3        8710 S CLOSTRIDIUM BOTULINUM
L4         406 S NEISSERIA GONORRHEAE
L5       73853 S FUSION PROTEIN OR HYBRID PROTEIN
L6         719 S MASTOCYTES
L7       14279 S BASOPHILS
L8        6169 S TETANUS TOXIN
L9        5949 S L2 AND L5
L10          5 S L9 AND L6
L11       1541 S L3 AND TYPE A
L12        383 S IGA PROTEASE
L13       4861 S L2 AND TOXIN
L14       1816 S L13 AND TRANSPORT
L15          1 S L14 AND L6
L16        406 S L14 AND L7
L17          6 S L16 AND L1
L18      15947 S DEGRANULATION

=> s l18 and prevention
L19       1464 L18 AND PREVENTION
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=> s l18 and l6
L20         147 L18 AND L6

=> s l18 and l7
L21        1780 L18 AND L7

=> s l20 and inhibition
L22          40 L20 AND INHIBITION

=> s l19 and inhibition
L23        1032 L19 AND INHIBITION

=> s l22 and l23
L24          13 L22 AND L23

=> d l24 ti abs ibib tot

L24  ANSWER 1 OF 13      MEDLINE on STN
TI   [Allergic risk of aprotinin].
     Le risque allergique de l'aprotinine.
AB   OBJECTIVE: To analyse the risk of anaphylactic reaction with the
     administration of aprotinin, either by i.v. route or as a biological
     sealant application and to propose updated guidelines in accordance with
     current data of the literature. DATA SOURCES: Search in the Medline data
     base of articles in French, English and German, published since 1960,
     using following key words: aprotinin, allergy, anaphylaxis. STUDY
     SELECTION: All categories of articles on this topic have been selected.
     DATA EXTRACTION: Articles have been analysed for history, incidence and
     mechanisms of anaphylactic reactions, symptomatology, factors of risk,
     diagnosis and precautions of use. DATA SYNTHESIS: Aprotinin is widely
     used for decreasing preoperative bleeding, especially in cardiac and
     orthopaedic surgery. This heterologue protein can cause anaphylactic
     reactions in 0.5 to 5.8% of patients, depending of the inclusion criteria.
     They are mediated by IgG and IgE antibodies. Aprotinin has also a direct,
     non specific, histaminoliberation effect. The clinical presentation
     includes various degrees of severity, up to cardiac arrest. Documented
     factors of risk are a previous parotinin administration, 15 days to 6
     months before, and intolerance to beef meat, white of egg, cheese and
     milk. The immediate biological diagnosis is obtained on assessing the
     degranulation of basophiles (histamine) and mastocytes
     (tryptase), as well as the concentration of anti-aprotinin antibodies
     (RAST IgE), with a test of inhibition. The secondary
     assessment, six weeks later, includes prick-tests and intradermoreactions
     if the former are negative. The mean precaution consists to search
     factors of risk at preanaesthetic assessment. The predictive value of
     systematic prick-tests has not yet been validated. Anti H1 and anti H2
     premedication is inefficient. A test dose can trigger a severe reaction.
     CONCLUSION: Considering a significant anaphylactic risk, aprotinin
     administration becomes only licit after a careful evaluation of the
     benefit-risk ratio.
ACCESSION NUMBER:   2000194364      MEDLINE
DOCUMENT NUMBER:    20194364   PubMed ID: 10730171
TITLE:              [Allergic risk of aprotinin].
                    Le risque allergique de l'aprotinine.
AUTHOR:             Laxenaire M C; Dewachter P; Pecquet C
CORPORATE SOURCE:   Departement d'anesthesie-reanimation, hopital central,
                    Nancy.
SOURCE:             ANNALES FRANCAISES D ANESTHESIE ET DE REANIMATION, (2000
                    Feb) 19 (2) 96-104.  Ref: 49
                    Journal code: 8213275. ISSN: 0750-7658.
PUB. COUNTRY:       France
DOCUMENT TYPE:      Journal; Article; (JOURNAL ARTICLE)
                    General Review; (REVIEW)
                    (REVIEW, TUTORIAL)
```

LANGUAGE: French
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200004
ENTRY DATE: Entered STN: 20000505
Last Updated on STN: 20000505
Entered Medline: 20000424

L24 ANSWER 2 OF 13 MEDLINE on STN
TI [Cromoglycic acid (disodium cromoglycate) and inhibitors of mast cell **degranulation**].
Acide cromoglicique (cromoglycate disodique) et inhibiteurs de la **degranulation** des **mastocytes**.
AB Cromoglycic acid (disodium cromoglycate) is a diacromone derived from khelline whose chief action in asthma is preventive, through **inhibition** of mastocyte **degranulation**. Since its digestive absorption is poor, it is given locally as a pulverulent aerosol. Cromoglycic acid is also used successfully in certain forms of ocular and nasal allergy. An oral preparation of cromoglycic acid is beginning to be used in food allergy and certain rectocolites. Trials are ongoing with several other substances, which have comparable properties and are active orally.
ACCESSION NUMBER: 84172265 MEDLINE
DOCUMENT NUMBER: 84172265 PubMed ID: 6324375
TITLE: [Cromoglycic acid (disodium cromoglycate) and inhibitors of mast cell **degranulation**].
Acide cromoglicique (cromoglycate disodique) et inhibiteurs de la **degranulation** des **mastocytes**.
AUTHOR: Advenier C; Ruff F
SOURCE: SEMAINE DES HOPITAUX, (1984 Feb 23) 60 (9) 659-64. Ref: 68
Journal code: 9410059.
PUB. COUNTRY: France
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
LANGUAGE: French
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198405
ENTRY DATE: Entered STN: 19900319
Last Updated on STN: 19970203
Entered Medline: 19840510

L24 ANSWER 3 OF 13 USPATFULL on STN
TI 1-alkyl or 1-cycloalkyltriazolo[4,3-a]quinazolin-5-ones as phosphodiesterase inhibitors
AB The invention relates to compounds of formula (I), ##STR1##

in which R.sup.1, R.sup.2 and R.sup.3 are as defined in the description, their use as medicaments, the process for their preparation and their use for the treatment of pathologies in which therapy by a PDE4 inhibitor is relevant.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
ACCESSION NUMBER: 2003:100149 USPATFULL
TITLE: 1-alkyl or 1-cycloalkyltriazolo[4,3-a]quinazolin-5-ones as phosphodiesterase inhibitors
INVENTOR(S): Guadilliere, Bernard, Nanterre, FRANCE
Lavalette, Remi, Longjumeau, FRANCE

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 2003069260	A1	20030410	
APPLICATION INFO.:	US 2002-211134	A1	20020802	(10)

	NUMBER	DATE

PRIORITY INFORMATION: EP 2001-402166 20010813
DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: PFIZER INC., PATENT DEPARTMENT, MS8260-1611, EASTERN POINT ROAD, GROTON, CT, 06340
NUMBER OF CLAIMS: 13
EXEMPLARY CLAIM: 1
LINE COUNT: 1081
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L24 ANSWER 4 OF 13 USPATFULL on STN
TI Immunogenic compounds with in particular an anti-cytokine effect, preparation process, pharmaceutical compositions and kits containing them
AB Cytokines, which are biologically inactive in humans but remain immunogenic, are used in pharmaceutical compositions to promote a neutralizing immune response against native cytokines when administrated to a subject in need thereof to treat homeostatic conditions and disorders associated with an overproduction of cytokines.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
ACCESSION NUMBER: 2002:246370 USPATFULL
TITLE: Immunogenic compounds with in particular an anti-cytokine effect, preparation process, pharmaceutical compositions and kits containing them
INVENTOR(S): Zagury, Daniel, Paris, FRANCE
Zagury, Jean-Fran.cedilla.ois, Paris, FRANCE
Bizzini, Bernard, Le Mesnil-Saint-Denis, FRANCE
PATENT ASSIGNEE(S): Neovacs, Paris, FRANCE (non-U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 6455045	B1	20020924
APPLICATION INFO.:	US 1999-317993		19990525 (9)

RELATED APPLN. INFO.: Continuation of Ser. No. US 1994-167867, filed on 27 Jun 1994, now patented, Pat. No. US 6093405

	NUMBER	DATE
PRIORITY INFORMATION:	FR 1991-7399	19910617

DOCUMENT TYPE: Utility
FILE SEGMENT: GRANTED
PRIMARY EXAMINER: Scheiner, Laurie
ASSISTANT EXAMINER: Parkin, Jeffrey S.
LEGAL REPRESENTATIVE: Browdy and Neimark
NUMBER OF CLAIMS: 11
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 0 Drawing Figure(s); 0 Drawing Page(s)
LINE COUNT: 1222
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L24 ANSWER 5 OF 13 USPATFULL on STN
TI Aerosolized anti-infectives, anti-inflammatories, and decongestants for the treatment of sinusitis
AB Pharmaceutical compositions are described that comprise one or more active ingredients selected from the group consisting of an anti-infective agent, anti-inflammatory agent, anti-mucolytic agent, antihistamine, an antiseptic, and antibiotic combinations or combinations of others of these classes of ingredients, and particularly to compositions formulated as a solution or suspension in a unit dose for aerosol administration to treat chronic sinusitis.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
ACCESSION NUMBER: 2002:119301 USPATFULL

TITLE: Aerosolized anti-infectives, anti-inflammatories, and decongestants for the treatment of sinusitis

INVENTOR(S): Osbakken, Robert S., Camarillo, CA, UNITED STATES
Hale, Mary Anne, Woodland Hills, CA, UNITED STATES
Leivo, Frederick T., Carpinteria, CA, UNITED STATES
Munk, James D., Camarillo, CA, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2002061281	A1	20020523
APPLICATION INFO.:	US 2001-942959	A1	20010831 (9)

RELATED APPLN. INFO.: Continuation-in-part of Ser. No. WO 2000-US18410, filed on 5 Jul 2000, UNKNOWN Continuation-in-part of Ser. No. US 2000-577623, filed on 25 May 2000, PENDING

	NUMBER	DATE
PRIORITY INFORMATION:	US 1999-142618P	19990706 (60)
	US 1999-142620P	19990706 (60)
	US 1999-142621P	19990706 (60)
	US 1999-142622P	19990706 (60)
	US 1999-142624P	19990706 (60)
	US 1999-142741P	19990706 (60)
	US 1999-142881P	19990706 (60)
	US 2000-193507P	20000403 (60)
	US 2000-193508P	20000403 (60)
	US 2000-193509P	20000403 (60)
	US 2000-193510P	20000403 (60)
	US 2000-194078P	20000403 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: MORGAN, LEWIS & BOCKIUS, 1800 M STREET NW, WASHINGTON, DC, 20036-5869
NUMBER OF CLAIMS: 37
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 1 Drawing Page(s)
LINE COUNT: 1893
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L24 ANSWER 6 OF 13 USPATFULL on STN
TI Inactive but immunogenic cytokines, pharmaceutical compositions containing same, and methods of treating homeostatic disorders associated with an overproduction of cytokines
AB Cytokines, which are biologically inactive in humans but remain immunogenic, are used in pharmaceutical compositions to promote a neutralizing immune response against native cytokines when administered to a subject in need thereof to treat homeostatic conditions and disorders associated with an overproduction of cytokines.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
ACCESSION NUMBER: 2000:94704 USPATFULL
TITLE: Inactive but immunogenic cytokines, pharmaceutical compositions containing same, and methods of treating homeostatic disorders associated with an overproduction of cytokines

INVENTOR(S): Zagury, Daniel, Paris, France
Zagury, Jean-Fran.cedilla.ois, Paris, France
Bizzini, Bernard, Le Mesnil-Saint-Denis, France
PATENT ASSIGNEE(S): Neovacs, Paris, France (non-U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 6093405		20000725
	WO 9222577		19921223

APPLICATION INFO.:	US 1994-167867	19940627	(8)
	WO 1992-FR544	19920617	
		19940627	PCT 371 date
		19940627	PCT 102(e) date

	NUMBER	DATE
PRIORITY INFORMATION:	FR 1991-7399	19910617

DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Eisenschenk, Frank C.
ASSISTANT EXAMINER: Parkin, Jeffrey S.
LEGAL REPRESENTATIVE: Browdy and Neimark
NUMBER OF CLAIMS: 12
EXEMPLARY CLAIM: 1
LINE COUNT: 1296
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L24 ANSWER 7 OF 13 USPATFULL on STN
TI Diazepinoindoles as phosphodiesterase 4 inhibitors
AB Diazepinoindoles of formula (I), ##STR1## wherein A is mono- to trisubstituted aryl or heteroaryl, and B is an --OR.sub.1 or --NR.sub.2 R.sub.3 group where R.sub.1, R.sub.2 and R.sub.3 are particularly hydrogen, and racemic forms, enantiomers and pharmaceutically acceptable salts thereof, as phosphodiesterase IV inhibitors, are disclosed.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
ACCESSION NUMBER: 1999:132811 USPATFULL
TITLE: Diazepinoindoles as phosphodiesterase 4 inhibitors
INVENTOR(S): Pascal, Yves, Rueil-Malmaison, France
Jacobelli, Henry, Parray-Vieille-Poste, France
Calvet, Alain, Ann Arbor, MI, United States
Payne, Adrian, Westerham, United Kingdom
Dahl, Svein G., Gif-sur-Yvette, France
PATENT ASSIGNEE(S): Jouveinal, Fresnes, France (non-U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 5972927		19991026	
	WO 9736905		19971009	
APPLICATION INFO.:	US 1998-952891		19981020	(8)
	WO 1997-FR557		19970327	
			19980407	PCT 371 date
			19980407	PCT 102(e) date

	NUMBER	DATE
PRIORITY INFORMATION:	FR 1996-4013	19960329

DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Shah, Mukund J.
ASSISTANT EXAMINER: Kifle, Bruck
LEGAL REPRESENTATIVE: Crissey, Todd M.
NUMBER OF CLAIMS: 23
EXEMPLARY CLAIM: 1
LINE COUNT: 2027
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L24 ANSWER 8 OF 13 USPATFULL on STN
TI Method of using relaxin as therapeutic or preventing agent
AB Methods of using relaxin (RLX), a peptide hormone of the insulin family, which has been found to produce effects on the walls of blood vessels, on blood clotting and on blood lipids and electrolytes, per se, and through the stimulation of the synthesis and release of the two powerful

substances: nitric oxide (NO) and atrial natriuretic peptide (ANP), are contemplated whereby RLX is administered to a patient for increasing blood flow, producing dilation of the arteries, influencing blood clotting and fibrinolysis, reducing blood lipids, inducing reduction of blood osmolarity and sodium concentration, and through NO for inhibiting release of histamine from mast cells. RLX is accordingly used as a therapeutic agent in methods for treating arteriosclerosis and vascular diseases, ischemia and thrombosis, hypertension and pregnancy's gestosis, and other diseases, or allergic and inflammatory disorders as dysfunctions in fluid and electrolyte balance.

ACCESSION NUMBER:	1999:110286 USPATFULL			
TITLE:	Method of using relaxin as therapeutic or preventing agent			
INVENTOR(S):	Bigazzi, Mario, Via del Palmerino No.11, Florence, Italy 50137			
	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 5952296		19990914	
	WO 9503822		19950209	
APPLICATION INFO.:	US 1995-403878		19950323	(8)
	WO 1994-IT124		19940726	
			19950323	PCT 371 date
			19950323	PCT 102(e) date
	NUMBER		DATE	
PRIORITY INFORMATION:	IT 1993-FI143		19930727	
	IT 1994-FI36		19940219	
	IT 1994-FI39		19940225	
DOCUMENT TYPE:	Utility			
FILE SEGMENT:	Granted			
PRIMARY EXAMINER:	Tsang, Cecilia J.			
ASSISTANT EXAMINER:	Delacroix-Muirheid, C.			
LEGAL REPRESENTATIVE:	McGlew and Tuttle, P.C.			
NUMBER OF CLAIMS:	37			
EXEMPLARY CLAIM:	1			
NUMBER OF DRAWINGS:	15 Drawing Figure(s); 5 Drawing Page(s)			
LINE COUNT:	750			

L24 ANSWER 9 OF 13 USPATFULL on STN

TI Triazole derivative and pharmaceutical use thereof

AB An agent for the prophylaxis and treatment of immune-related diseases, in particular, immunosuppressant, an agent for the prophylaxis and treatment of allergic diseases, an agent for the prophylaxis and treatment of eosinophil-related diseases and an eosinophilia inhibitor, comprising, as an active ingredient, a series of triazole derivatives of the following formula (I) ##STR1## or the following formula (III) ##STR2## wherein each symbol is as defined in the specification, or a pharmaceutically acceptable salt thereof. A novel monocyclic or bicyclic triazole derivative. The agent for the prophylaxis and treatment of immune-related diseases, in particular, immunosuppressant, the agent for the prophylaxis and treatment of allergic diseases, the agent for the prophylaxis and treatment of eosinophil-related diseases, the eosinophilia inhibitor and the novel triazole derivative of the present invention all, have superior eosinophilia-inhibitory action and lymphocyte activation-inhibitory action. They are low toxic and persistent in action. They are particularly effective in the treatment of accumulation and activation of eosinophil and lymphocytes, inflammatory respiratory tract diseases, eosinophil-related diseases such as eosinophilia, and immune-related diseases.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

ACCESSION NUMBER: 1998:51621 USPATFULL
TITLE: Triazole derivative and pharmaceutical use thereof
INVENTOR(S): Akahoshi, Fumihiko, Osaka, Japan
Okada, Takehiro, Osaka, Japan
Takeda, Shinji, Osaka, Japan
Naito, Youichiro, Osaka, Japan
Fukaya, Chikara, Osaka, Japan
Kuwahara, Shigeki, Osaka, Japan
Kajii, Masahiko, Osaka, Japan
Nishimura, Hiroko, Osaka, Japan
Sugiura, Masanori, Osaka, Japan
PATENT ASSIGNEE(S): The Green Cross Corporation, Osaka, Japan (non-U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 5750545		19980512	
	WO 9503286		19950202	
APPLICATION INFO.:	US 1996-586787		19960123	(8)
	WO 1994-JP1215		19940722	
			19960123	PCT 371 date
			19960123	PCT 102(e) date

	NUMBER	DATE
PRIORITY INFORMATION:	JP 1993-182522	19930723
	JP 1993-182544	19930723
	JP 1993-193460	19930804

DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Raymond, Richard L.
LEGAL REPRESENTATIVE: Sughrue, Mion, Zinn, Macpeak & Seas, PLLC
NUMBER OF CLAIMS: 17
EXEMPLARY CLAIM: 1
LINE COUNT: 3304
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L24 ANSWER 10 OF 13 USPATFULL on STN
TI N-acyl derivatives of aminoalcohols with polycarboxylic acids able to modulate mast cells in inflammatory processes having neuroimmunogenic origin
AB N-acyl derivatives of aminoalcohols with bicarboxylic or tricarboxylic acids able to modulate the **degranulation** process consequent to the mast cells activation in inflammatory processes caused by supramaximal stimuli of neurogenic and immunogenic origin.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
ACCESSION NUMBER: 97:29497 USPATFULL
TITLE: N-acyl derivatives of aminoalcohols with polycarboxylic acids able to modulate mast cells in inflammatory processes having neuroimmunogenic origin
INVENTOR(S): Della Valle, Francesco, Padua, Italy
Lorenzi, Silvana, Padua, Italy
Marcolongo, Gabriele, Carrara San Giorgio, Italy
PATENT ASSIGNEE(S): Lifegroup S.p.A., Rome, Italy (non-U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 5618842		19970408	
APPLICATION INFO.:	US 1994-265460		19940624	(8)
RELATED APPLN. INFO.:	Continuation-in-part of Ser. No. US 1992-998792, filed on 30 Dec 1992, now abandoned			

	NUMBER	DATE

PRIORITY INFORMATION:	IT 1991-MI3509	19911231
DOCUMENT TYPE:	Utility	
FILE SEGMENT:	Granted	
PRIMARY EXAMINER:	Cintins, Marianne	
ASSISTANT EXAMINER:	MacMillan, Keith	
LEGAL REPRESENTATIVE:	Watson Cole Stevens Davis, P.L.L.C.	
NUMBER OF CLAIMS:	16	
EXEMPLARY CLAIM:	1	
LINE COUNT:	1384	

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L24 ANSWER 11 OF 13 USPATFULL on STN

TI Use of zinc acexamate in the prophylaxis of gastropathy induced by non-steroidal anti-inflammatory drugs

AB Zinc acexamate acts by increasing the synthesis of mucus, reinforces the mucous barrier, improves the microcirculation and increases the synthesis of prostaglandins in the gastric mucous membrane, whereby it is effective in the treatment of said gastropathy, contrary to the results obtained with antiacids or antisecretory agents.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

ACCESSION NUMBER:	92:63848 USPATFULL
TITLE:	Use of zinc acexamate in the prophylaxis of gastropathy induced by non-steroidal anti-inflammatory drugs
INVENTOR(S):	Vinas, Antonio B., Barcelona, Spain
PATENT ASSIGNEE(S):	Laboratorios Vinas, S.A., Barcelona, Spain (non-U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 5135925		19920804
APPLICATION INFO.:	US 1991-644484		19910118 (7)

RELATED APPLN. INFO.:	Continuation of Ser. No. US 1990-505490, filed on 6 Apr 1990, now abandoned
DOCUMENT TYPE:	Utility
FILE SEGMENT:	Granted
PRIMARY EXAMINER:	Friedman, S. J.
LEGAL REPRESENTATIVE:	Dressler, Goldsmith, Shore, Sutker & Milnamow, Ltd.
NUMBER OF CLAIMS:	15
EXEMPLARY CLAIM:	1
LINE COUNT:	357

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L24 ANSWER 12 OF 13 USPATFULL on STN

TI Injectable glycoproteins containing terminal "C" ends of human immunoglobulins

AB Pharmaceutical compositions comprise, as their essential active ingredients human immunoglobulin D molecules or the terminal C ends of the heavy chains of such molecules, preferably the Fc and F'c fragments. These compositions, which are usually in the form of sterile injectable solutions, have anti-allergic, anti-inflammatory and immunodepressant properties.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

ACCESSION NUMBER:	75:70466 USPATFULL
TITLE:	Injectable glycoproteins containing terminal "C" ends of human immunoglobulins
INVENTOR(S):	Fontaine, Michel J., 448, rue Paradis, 13008 Marseilles, France

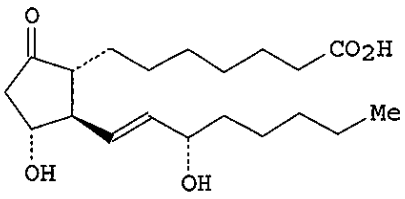
	NUMBER	KIND	DATE
PATENT INFORMATION:	US 3928580		19751223

APPLICATION INFO.: US 1974-453019 19740319 (5)

	NUMBER	DATE
PRIORITY INFORMATION:	FR 1973-11455	19730322

DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Gotts, Lewis
ASSISTANT EXAMINER: Suyat, Reginald J.
LEGAL REPRESENTATIVE: Brooks Haidt Haffner & Delahunty
NUMBER OF CLAIMS: 12
EXEMPLARY CLAIM: 1
LINE COUNT: 380
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L24 ANSWER 13 OF 13 HCAPLUS COPYRIGHT 2003 ACS on STN
TI Effects of prostaglandin E1 on mastocyte **degranulation** and heparin liberation elicited by lipid suspensions
GI



I

AB PGE1 (I) [745-65-3] (3 .times. 10-4M) had a protective effect on the spontaneous **degranulation** of **mastocytes** after incubation for 40 min at 37.degree.. However, I decreased but did not prevent the **degranulation**, accompanied by the liberation of heparin [9005-49-6], in the presence of a lipidic suspension. The action of I was compared with that of cyclic AMP [60-92-4] and cyclic GMP [7665-99-8].

ACCESSION NUMBER: 1980:462034 HCAPLUS
DOCUMENT NUMBER: 93:62034
TITLE: Effects of prostaglandin E1 on mastocyte **degranulation** and heparin liberation elicited by lipid suspensions
AUTHOR(S): Guillosson, J. J.; Piette, C.; Piette, M.
CORPORATE SOURCE: Lab. d'Hematol., UER Biol. Hum. Exp., Paris, F 75270/6, Fr.
SOURCE: Annales Pharmaceutiques Francaises (1980), 38(1), 15-20
CODEN: APFRAD; ISSN: 0003-4509
DOCUMENT TYPE: Journal
LANGUAGE: French

=> d his

(FILE 'HOME' ENTERED AT 12:49:06 ON 21 NOV 2003)

FILE 'MEDLINE, USPATFULL, WPIDS, JICST-EPLUS, FSTA, HCAPLUS' ENTERED AT 12:53:40 ON 21 NOV 2003

L1 898 S IGE FRAGMENT
L2 59183 S IGE
L3 8710 S CLOSTRIDIUM BOTULINUM
L4 406 S NEISSERIA GONORRHEAE
L5 73853 S FUSION PROTEIN OR HYBRID PROTEIN

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L6          719 S MASTOCYTES
L7        14279 S BASOPHILS
L8         6169 S TETANUS TOXIN
L9         5949 S L2 AND L5
L10           5 S L9 AND L6
L11        1541 S L3 AND TYPE A
L12         383 S IGA PROTEASE
L13        4861 S L2 AND TOXIN
L14        1816 S L13 AND TRANSPORT
L15           1 S L14 AND L6
L16         406 S L14 AND L7
L17           6 S L16 AND L1
L18       15947 S DEGRANULATION
L19        1464 S L18 AND PREVENTION
L20         147 S L18 AND L6
L21        1780 S L18 AND L7
L22          40 S L20 AND INHIBITION
L23        1032 S L19 AND INHIBITION
L24          13 S L22 AND L23

=>  s IgE () transport () basophil () toxin
L25           0 IGE (W) TRANSPORT (W) BASOPHIL (W) TOXIN

=> s l2 and allergic response
L26        1419 L2 AND ALLERGIC RESPONSE

=> s toxin transport
L27          99 TOXIN TRANSPORT

=> s l27 and l1
L28           0 L27 AND L1

=> s l2 and transport to basophil
L29           0 L2 AND TRANSPORT TO BASOPHIL

=> s IgE () transport () basophil
L30           0 IGE (W) TRANSPORT (W) BASOPHIL

=> s l3 and l2
L31         317 L3 AND L2

=> s l31 and l18
L32           9 L31 AND L18

=> d l32 ti abs ibib tot

L32  ANSWER 1 OF 9     MEDLINE on STN
TI   Influence of Clostridium botulinum C2 toxin on Fc
     epsilonRI-mediated secretion and tyrosine phosphorylation in RBL cells.
AB   We studied the effects of the binary Clostridium
     botulinum C2 toxin on stimulated [3H]serotonin release and protein
     tyrosine phosphorylation in RBL 2H3 hm1 cells.  Actin was specifically
     ADP-ribosylated by C2 toxin in intact cells resulting in a 2-3 fold
     increase in antigen- or calcium ionophore (A23187)-induced
     degranulation.  The effects of C2 toxin were time- and
     concentration-dependent.  Toxin treatment, which dramatically changes the
     morphology of RBL cells, was not sufficient to induce mediator release in
     the absence of activators of secretion.  Antigen- and A23187-stimulated
     tyrosine phosphorylation of 60-80 kDa and 110-120 kDa proteins was reduced
     or blocked after C2 toxin incubation.  Treatment of RBL cells with the
     tyrosine phosphatase inhibitor pervanadate reversed the inhibitory effect
     of C2 toxin on stimulated protein tyrosine phosphorylation indicating
     activation of phosphatases by C2 toxin.  The data indicate that
     disassembly of the actin cytoskeleton by C2 toxin facilitates Fc
```

epsilonRI-mediated signal-secretion coupling and suggest a role of the actin cytoskeleton in phosphatase regulation in RBL cells.

ACCESSION NUMBER: 1998209675 MEDLINE
DOCUMENT NUMBER: 98209675 PubMed ID: 9550305
TITLE: Influence of **Clostridium botulinum** C2 toxin on Fc epsilonRI-mediated secretion and tyrosine phosphorylation in RBL cells.
AUTHOR: Prepens U; Barth H; Wilting J; Aktories K
CORPORATE SOURCE: Institut fur Pharmakologie und Toxikologie der Albert-Ludwigs-Universitat Freiburg, Germany.
SOURCE: NAUNYN-SCHMIEDEBERGS ARCHIVES OF PHARMACOLOGY, (1998 Mar) 357 (3) 323-30.
Journal code: 0326264. ISSN: 0028-1298.
PUB. COUNTRY: GERMANY: Germany, Federal Republic of
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199805
ENTRY DATE: Entered STN: 19980609
Last Updated on STN: 19980609
Entered Medline: 19980528

L32 ANSWER 2 OF 9 MEDLINE on STN
TI Inhibition of Fc epsilon-RI-mediated activation of rat basophilic leukemia cells by Clostridium difficile toxin B (monoglucosyltransferase).
AB Treatment of rat basophilic leukemia (RBL) 2H3-hm1 cells with Clostridium difficile toxin B (2 ng/ml), which reportedly depolymerizes the actin cytoskeleton, blocked [3H]serotonin release induced by 2,4-dinitrophenyl-bovine serum albumin, carbachol, mastoparan, and reduced ionophore A23187-stimulated **degranulation** by about 55-60%. In lysates of RBL cells, toxin B 14C-glucosylated two major and one minor protein. By using two-dimensional gel electrophoresis and immunoblotting, RhoA and Cdc42 were identified as protein substrates of toxin B. In contrast to toxin B, **Clostridium botulinum** transferase C3 that selectively inactivates RhoA by ADP-ribosylation did not inhibit **degranulation** up to a concentration of 150 microg/ml. Antigen-stimulated tyrosine phosphorylation of a 110-kDa protein was inhibited by toxin B as well as by the phosphatidylinositol 3-kinase inhibitor wortmannin. Depolymerization of the microfilament cytoskeleton of RBL cells by C. botulinum C2 toxin or cytochalasin D resulted in an increased [3H]serotonin release induced by antigen, carbachol, mastoparan, or by calcium ionophore A23187, but without affecting toxin B-induced inhibition of **degranulation**. The data indicate that toxin B inhibits activation of RBL cells by glucosylation of low molecular mass GTP-binding proteins of the Rho subfamily (most likely Cdc42) by a mechanism not involving the actin cytoskeleton.

ACCESSION NUMBER: 96205904 MEDLINE
DOCUMENT NUMBER: 96205904 PubMed ID: 8631752
TITLE: Inhibition of Fc epsilon-RI-mediated activation of rat basophilic leukemia cells by Clostridium difficile toxin B (monoglucosyltransferase).
AUTHOR: Prepens U; Just I; von Eichel-Streiber C; Aktories K
CORPORATE SOURCE: Institut fur Pharmakologie und Toxikologie der Albert-Ludwigs-Universitat Freiburg, Germany.
SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (1996 Mar 29) 271 (13) 7324-9.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199607
ENTRY DATE: Entered STN: 19960715
Last Updated on STN: 19980206

Entered Medline: 19960703

L32 ANSWER 3 OF 9 USPATFULL on STN
TI Sphingolipid derivatives and their methods of use
AB Derivatives of sphingolipids of the formula: ##STR1##

are provided wherein the substituents are as defined in the specification and wherein there is at least one R.sup.2 substituent in the sphingolipid derivative. The compounds are useful in the treatment of of abnormal cell proliferation, including benign and malignant tumors, the promotion of cell differentiation, the induction of apoptosis, the inhibition of protein kinase C, and the treatment of inflammatory conditions, psoriasis, inflammatory bowel disease as well as proliferation of smooth muscle cells in the course of development of plaques in vascular tissue. The invention also includes a method for triggering the release of cytochrome c from mitochondria that includes administering an effective amount of a sphingolipid or its derivative or prodrug to a host in need thereof. Further, the invention provides a method for treating bacterial infections, including those that influence colon cancer and other disorders of the intestine, that includes administering an effective amount of one of the active compounds identified herein.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

ACCESSION NUMBER:	2003:228401 USPATFULL
TITLE:	Sphingolipid derivatives and their methods of use
INVENTOR(S):	Liotta, Dennis C., McDonough, GA, United States Merrill, Jr., Alfred H., Stone Mountain, GA, United States Keane, Thomas E., Dunwoody, GA, United States Bhalla, Kapil N., Atlanta, GA, United States Schmelz, Eva M, Atlanta, GA, United States (4)
PATENT ASSIGNEE(S):	Emory University, Atlanta, GA, United States (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 6610835	B1	20030826	
APPLICATION INFO.:	US 1999-249211		19990212	(9)

	NUMBER	DATE
PRIORITY INFORMATION:	US 1998-74536P	19980212 (60)

DOCUMENT TYPE:	Utility
FILE SEGMENT:	GRANTED
PRIMARY EXAMINER:	Wilson, James O.
ASSISTANT EXAMINER:	Maier, Leigh C.
LEGAL REPRESENTATIVE:	King & Spalding LLP, Knowles, Sherry M.
NUMBER OF CLAIMS:	42
EXEMPLARY CLAIM:	1
NUMBER OF DRAWINGS:	18 Drawing Figure(s); 16 Drawing Page(s)
LINE COUNT:	4123

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L32 ANSWER 4 OF 9 USPATFULL on STN
TI Gene products that regulate glucose response in cells
AB The present invention describes the identification of numerous genes, both known and unknown, that play an important role in the ability of cell to respond to glucose stimulation under physiologic conditions. These genes may be used to enhance, stabilize or introduce glucose-responsiveness in a host cell, in particular, a host cell that secretes insulin. In addition, these genes may be used as targets for drug screening and as diagnostic indicators for the loss of glucose-responsiveness.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
ACCESSION NUMBER: 2003:213783 USPATFULL
TITLE: Gene products that regulate glucose response in cells
INVENTOR(S): Newgard, Christopher B., Dallas, TX, UNITED STATES
Jensen, Per Bo, Ballerup, DENMARK

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 2003148421	A1	20030807	
APPLICATION INFO.:	US 2002-80381	A1	20020219	(10)

	NUMBER	DATE	
PRIORITY INFORMATION:	US 2001-270251P	20010220	(60)
	US 2001-274706P	20010309	(60)
	US 2001-291354P	20010515	(60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: Steven L. Highlander, Fullbright & Jaworski L.L.P., Suite 2400, 600 Congress Avenue, Austin, TX, 78701
NUMBER OF CLAIMS: 55
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 12 Drawing Page(s)
LINE COUNT: 6287
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L32 ANSWER 5 OF 9 USPATFULL on STN
TI Hybrid protein for inhibiting the **degranulation** of mastocytes and the use thereof
AB A hybrid protein contains a protein that binds to a receptor of mastocytes and basophils and is endocyted by them. The protein can be **IgE**; **IgE** fragment; **IgE** Fc fragment; antibody against **IgE** receptor of mastocytes and basophils; fragment of the antibody against the **IgE** receptor of mastocytes and basophils; antibody against mastocyte specific potassium channel; and mast cell degranulating peptide. The hybrid protein also contains a protease cleaving proteins of the secretion process of the mastocytes and basophils so as to inhibit the secretion process without killing the mastocytes and basophils. The protease can be light chain **Clostridium botulinum** toxin; proteolytically active fragment of the light chain of a **Clostridium botulinum** toxin containing an amino acid sequence His-Xaa-Xaa-Xaa-His-Xaa-Xaa-His wherein Xaa is an amino acid; light chain of the tetanus toxin; proteolytically active fragment of the light chain of the tetanus toxin containing His-Asp-Leu-Ile-His-Val-Leu-His; IgA protease of Neisseria gonorrhoeae; and proteolytic domain of the IgA protease of Neisseria gonorrhoeae.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
ACCESSION NUMBER: 2003:86306 USPATFULL
TITLE: Hybrid protein for inhibiting the **degranulation** of mastocytes and the use thereof
INVENTOR(S): Bigalke, Hans, Hannover, GERMANY, FEDERAL REPUBLIC OF
Frevert, Jurgen, Berlin, GERMANY, FEDERAL REPUBLIC OF
PATENT ASSIGNEE(S): BioteCon Gesellschaft fur biotechnologische Entwicklung und consulting mbH, Berlin, DE, 10589 (non-U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 2003059912	A1	20030327	
APPLICATION INFO.:	US 2002-64903	A1	20020827	(10)
RELATED APPLN. INFO.:	Continuation-in-part of Ser. No. US 2001-700540, filed			

on 19 Jan 2001, PENDING A 371 of International Ser. No. WO 1999-EP3272, filed on 12 May 1999, UNKNOWN

	NUMBER	DATE
PRIORITY INFORMATION:	DE 1998-19821285	19980513

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: GUDRUN E. HUCKETT, LONSSTR. 53, WUPPERTAL, 42289
NUMBER OF CLAIMS: 11
EXEMPLARY CLAIM: 1
LINE COUNT: 576
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L32 ANSWER 6 OF 9 USPATFULL on STN
TI Methods for evaluating risk of developing periodontitis
AB The subject invention relates to methods and kits for detecting or evaluating risk of presently or later developing active periodontitis, comprising: (a) collecting gingival crevicular fluid; (b) measuring the amount in the gingival crevicular fluid of IgA; (c) measuring the amount in the gingival crevicular fluid of a marker for polymorphonuclear leukocytes; (d) comparing a ratio of the amounts obtained from steps (b) and (c) to a standard.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
ACCESSION NUMBER: 94:112896 USPATFULL
TITLE: Methods for evaluating risk of developing periodontitis
INVENTOR(S): Singer, Jr., Robert E., Fairfield, OH, United States
PATENT ASSIGNEE(S): The Procter & Gamble Company, Cincinnati, OH, United States (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 5376532		19941227	
APPLICATION INFO.:	US 1992-947657		19920918	(7)

DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Bidwell, Carol E.
LEGAL REPRESENTATIVE: Crosmun, Jean R., Suter, David L., Graff, Mick B.
NUMBER OF CLAIMS: 6
EXEMPLARY CLAIM: 1
LINE COUNT: 1053
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L32 ANSWER 7 OF 9 HCAPLUS COPYRIGHT 2003 ACS on STN
TI Inhibiting the **degranulation** in mastocytes using a hybrid protein comprising a receptor-binding protein fused to a protease cleaving a protein of the secretion process
AB A hybrid protein is provided contg. a protein that binds to a receptor of mastocytes and basophils and is endocytosed by them. The protein can be **IgE**, **IgE** fragment, **IgE** Fc fragment, antibody against the **IgE** receptor of mastocytes and basophils, a fragment of the antibody against the **IgE** receptor of mastocytes and basophils, an antibody against mastocyte-specific potassium channel, or mast cell degranulating peptide. The hybrid protein also contains a protease which cleaves proteins of the secretion process of the mastocytes and basophils so as to inhibit the secretion process without killing the mastocytes and basophils. The protease can be the light chain of **Clostridium botulinum** toxin or its proteolytic fragments contg. a His-Xaa-Xaa-Xaa-His-Xaa-Xaa-His sequence, the light chain of the tetanus toxin or proteolytically active fragment of the light chain contg. His-Asp-Leu-Ile-His-Val-Leu-His, or an IgA protease of Neisseria gonorrhoeae and its proteolytic domain. Thus, a hybrid protein comprising **IgE** fused to the light chain of either **Clostridium**

botulinum toxin or tetanus toxin prevents allergic shock caused by dying mastocytes.

ACCESSION NUMBER: 2003:241912 HCAPLUS
DOCUMENT NUMBER: 138:265639
TITLE: Inhibiting the **degranulation** in mastocytes using a hybrid protein comprising a receptor-binding protein fused to a protease cleaving a protein of the secretion process
INVENTOR(S): Bigalke, Hans; Frevert, Jurgen
PATENT ASSIGNEE(S): Biotecon Gesellschaft Fur Biotechnologische Entwicklung Und Consulting Mbh, Germany
SOURCE: U.S. Pat. Appl. Publ., 7 pp., Cont.-in-part of U.S. Ser. No. 700,540.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2003059912	A1	20030327	US 2002-64903	20020827
WO 9958571	A2	19991118	WO 1999-EP3272	19990512
WO 9958571	A3	20000203		

W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: DE 1998-19821285 A 19980513
WO 1999-EP3272 W 19990512
US 2001-700540 A2 20010119

L32 ANSWER 8 OF 9 HCAPLUS COPYRIGHT 2003 ACS on STN
TI Hybrid protein for inhibiting the **degranulation** of mastocytes and the use thereof
AB The invention relates to a hybrid protein comprising or comprised of (i) a known protein which binds to mastocytes and/or basophils in a known manner and/or is absorbed thereby, and of (ii) a protease which splits one or more proteins of the secretory app. of the mastocytes and/or basophils. The examples discuss the synthesis of these hybrid proteins using expression vectors expressed in E. coli.

ACCESSION NUMBER: 1999:736768 HCAPLUS
DOCUMENT NUMBER: 131:332099
TITLE: Hybrid protein for inhibiting the **degranulation** of mastocytes and the use thereof
INVENTOR(S): Bigalke, Hans; Frevert, Jurgen
PATENT ASSIGNEE(S): Biotecon Gesellschaft fur Biotechnologische Entwicklung und Consulting m.b.H, Germany
SOURCE: PCT Int. Appl., 22 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9958571	A2	19991118	WO 1999-EP3272	19990512

WO 9958571	A3	20000203			
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2331274	AA	19991118	CA 1999-2331274	19990512	
AU 9942605	A1	19991129	AU 1999-42605	19990512	
AU 755513	B2	20021212			
BR 9910359	A	20010109	BR 1999-10359	19990512	
EP 1084146	A2	20010321	EP 1999-950347	19990512	
EP 1084146	B1	20021113			
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, FI					
JP 2002514659	T2	20020521	JP 2000-548373	19990512	
AT 227739	E	20021115	AT 1999-950347	19990512	
ES 2187200	T3	20030516	ES 1999-950347	19990512	
RU 2214420	C2	20031020	RU 2000-131217	19990512	
NO 2000005637	A	20001108	NO 2000-5637	20001108	
HK 1036994	A1	20030221	HK 2001-106685	20010921	
US 2003059912	A1	20030327	US 2002-64903	20020827	
PRIORITY APPLN. INFO.:			DE 1998-19821285 A	19980513	
			WO 1999-EP3272 W	19990512	
			US 2001-700540 A2	20010119	

L32 ANSWER 9 OF 9 HCAPLUS COPYRIGHT 2003 ACS on STN

TI Influence of **Clostridium botulinum** C2 toxin on Fc.epsilon.RI-mediated secretion and tyrosine phosphorylation in RBL cells

AB The authors studied the effects of the binary **Clostridium botulinum** C2 toxin on stimulated [3H]serotonin release and protein tyrosine phosphorylation in RBL 2H3 hm1 cells. Actin was specifically ADP-ribosylated by C2 toxin in intact cells resulting in a 2-3 fold increase in antigen- or calcium ionophore (A23187)-induced **degranulation**. The effects of C2 toxin were time- and concn.-dependent. Toxin treatment, which dramatically changes the morphol. of RBL cells, was not sufficient to induce mediator release in the absence of activators of secretion. Antigen- and A23187-stimulated tyrosine phosphorylation of 60-80 kDa and 110-120 kDa proteins was reduced or blocked after C2 toxin incubation. Treatment of RBL cells with the tyrosine phosphatase inhibitor pervanadate reversed the inhibitory effect of C2 toxin on stimulated protein tyrosine phosphorylation indicating activation of phosphatases by C2 toxin. The data indicate that disassembly of the actin cytoskeleton by C2 toxin facilitates Fc.epsilon.RI-mediated signal-secretion coupling and suggest a role of the actin cytoskeleton in phosphatase regulation in RBL cells.

ACCESSION NUMBER: 1998:137930 HCAPLUS
DOCUMENT NUMBER: 128:267074
TITLE: Influence of **Clostridium botulinum** C2 toxin on Fc.epsilon.RI-mediated secretion and tyrosine phosphorylation in RBL cells
AUTHOR(S): Prepens, Ulrike; Barth, Holger; Wilting, Jorg; Aktories, K.
CORPORATE SOURCE: Institut fur Pharmakologie und Toxikologie der Albert-Ludwigs-Universitat Freiburg, Hermann-Herder-Strasse 5, Freiburg, D-79104, Germany
SOURCE: Naunyn-Schmiedeberg's Archives of Pharmacology (1998), 357(3), 323-330
CODEN: NSAPCC; ISSN: 0028-1298
PUBLISHER: Springer-Verlag
DOCUMENT TYPE: Journal
LANGUAGE: English

REFERENCE COUNT: 59 THERE ARE 59 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

WEST

Freeform Search

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US Pre-Grant Publication Full-Text Database
JPO Abstracts Database
EPO Abstracts Database
Derwent World Patents Index
IBM Technical Disclosure Bulletins

Term: inhibition same degraulation mastocyte

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Set Name side by side	Query	Hit Count	Set Name result set
DB=USPT; PLUR=YES; OP=OR			
L11	L10 and l5	59	L11
L10	L9 and inhibit degranulation	53547	L10
L9	hybrid protein and binding receptor	166550	L9
L8	clostriduim botulinum toxin and L7	15971	L8
L7	tetanus toxin and L6	17220	L7
L6	l5 and hybrid protein	141489	L6
L5	inhibition same degraulation mastocyte	91	L5
L4	inhibition same degraulation same mastocyte	0	L4
L3	inhibition near degraulation near mastocyte	0	L3
L2	inhibition and degraulation and mastocyte	0	L2
L1	inhibition adj degraulation adj mastocyte	0	L1

END OF SEARCH HISTORY

WEST

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L11: Entry 1 of 59 File: USPT Nov 18, 2003

DOCUMENT-IDENTIFIER: US 6649166 B1
TITLE: Peptides and proteins for desensitizing subjects allergic to bee venom and compositions containing same

Abstract Text (1):
The invention concerns peptides and proteins for desensitizing specifically the vast majority of subjects allergic to bee venom and compositions containing said peptides or proteins. The peptides are selected in the group consisting of: the fragment (1) corresponding to positions P85-97 of the major bee venom allergen, the fragment (2) corresponding to positions P81-93 of the major bee venom allergen, the fragment (3) corresponding to positions P94-106 of the major bee venom allergen, the fragment (4) corresponding to positions P76-88 of the major bee venom allergen, the fragment (5) corresponding to positions P77-94 of the major bee venom allergen, and the fragment (6) corresponding to positions P122-134 of the major bee venom allergen, fragments (I) and (2) forming group (1); fragment (3) forming group (II); fragments (4) and (4) forming group (III) and fragment (6) forming group IV and the mutated fragments of said fragments (1) to (6) which have a binding activity with MHC class (II) molecules identical or higher than those of said fragments (1) to (6). The invention also concerns compositions containing said peptides or proteins.

Brief Summary Text (1):
The present invention relates to peptides and proteins capable of desensitizing, in a specific manner, the great majority of subjects allergic to bee venom, and to compositions containing said peptides or proteins.

Brief Summary Text (4):
IgEs appear gradually under the repeated action of stings and before any symptom becomes apparent. Although the bee venom comprises numerous peptides and proteins, all the components do not appear to be allergenic (4). Melittin, for example, induces IgEs in only 30% of patients, whereas the proportion increases to more than 90% for phospholipase A2 (PLA2) which is, as a result, considered to be the major allergen (API m1). The protein sequence of bee venom phospholipase A2 (API m1) is illustrated in FIG. 1 (SEQ ID NO: 8); this sequence is deduced from that of the complementary cDNA (36).

Brief Summary Text (5):
IgEs possess the property of binding, via their Fc fragment, to receptors situated on the tissue mastocytes and the blood basophils. When the allergen forms a complex with the specific IgEs bound to the membrane of the basophils or mastocytes, it causes degranulation of the cells and the release of molecules which are responsible for the principal manifestations observed during an allergic accident. IgEs are not solely responsible for the allergy because although the IgE level is an indicator for the disease, it has no diagnostic value for the state of the patients. It is not rare for patients to have high IgE levels without showing symptoms. The appearance of IgEs in allergic patients results from the production of type TH2 cytokines such as IL-4, IL-5 and IL-13 and is inhibited by the synthesis of IFN-.gamma. (6).

Brief Summary Text (9):
The CD4.sup.+ T lymphocytes possess a rearranged T receptor which allows them to selectively recognize peptide fragments derived from the degradation of the antigen by the presenting cells and presented by the Major Histocompatibility Complex class II (MHC II) molecules (15). The determinants which these peptide fragments carry and which the T lymphocytes effectively recognize are called T epitopes.

Brief Summary Text (11):
It has indeed been observed in vivo in mice for the allergens Fel d1 (cat hair), Der p1 (acarian: Dermatophagoides pterissimus) and Bet v1 (birch pollen) that the nasal, oral or subcutaneous administration of peptides carrying T epitopes of these allergens inhibits the activation of the specific T lymphocytes (16-18) and modulates the allergic reaction (16, 18).

Brief Summary Text (13):
Several types of molecule are already being studied, including in the context of bee venom allergy and consist either of peptide fragments or of modified proteins.

Brief Summary Text (22):
The approach followed by these various authors (23, 24 and 30) is based on cellular tests and not on binding tests. The results observed show that the active peptides vary according to the patients. In the latter three studies, the peptides containing the zone 80-90 are those which are most often a T epitope. They also show that the lymphocytes of several patients are stimulated by peptides containing the C-terminal portion of API m1.

Brief Summary Text (25):
Modified Proteins

Brief Summary Text (30):
The molecules of the major histocompatibility complex (MHC) class II (HLA II in man) are heterodimers expressed on presenting cells and present the T epitopes of the antigens to the CD4.sup.+ T lymphocytes. These molecules are capable of binding a large repertoire of peptides having very different sequences, which allows them to present several peptides per antigen to the T cells.

Brief Summary Text (32):
Each allele possesses its own binding properties. It therefore binds a repertoire of peptides specific to it and which differs from that for another allele, even on the same antigen. The broad specificity of the HLA II molecules and the existence of several isoforms and of a high polymorphism mean that many different fragments of the antigen can be presented to the T lymphocytes.

Brief Summary Text (35):
The 2nd gene encodes the HLA-DRB3, -DRB4 and -DRB5 molecules which are HLA-DR molecules whose .beta. chain is not encoded by the DRB1 gene. Although less well known than the molecules derived from the 1st gene, these HLA molecules are functional and are capable of presenting peptides to the T lymphocytes (56-59). Their main advantage for the immunotherapy is that alleles such as DRB3*0101 (9.2%), DRB4*0101 (28.4%) and DRB5*0101 (7.9%) are very frequent in the Caucasian population. They cover, on their own, 45% of the gene frequency. They are systematically associated with another HLA-DR molecule and can therefore complement its specificity. A strong binding disequilibrium exists between the 1st and 2nd gene, that is to say that a 2nd gene is very often associated with particular alleles of the 1st gene. The set of DR pseudogene and genes present on the same chromosome constitutes a DR haplotype (FIG. 5). Each haplotype is defined by the second DR molecule which characterizes it.

Brief Summary Text (39):
The subject of the present invention is peptides capable of desensitizing a subject allergic to bee venom, characterized in that they are selected from the group consisting of: fragment (1) corresponding to positions P85-97 of the major bee venom allergen, fragment (2) corresponding to positions P81-93 of the major bee venom allergen, fragment (3) corresponding to positions P94-106 of the major bee venom allergen, fragment (4) corresponding to positions P76-88 of the major bee venom allergen, fragment (5) corresponding to positions P77-94 of the major bee venom allergen, fragment (6) corresponding to positions P122-134 of the major bee venom allergen, and the mutated fragments of said fragments (1) to (6) which exhibit an MHC class II molecule binding activity identical to or higher than those of said fragments (1) to (6).

Brief Summary Text (43):
The site for binding of the peptides to the class II molecules is situated between the .alpha. helices of the .alpha.1 and .alpha.2 domains and forms a groove which is open at both ends. This opening allows the binding of peptides with varying sizes, in general from 13 to 25 amino acids. The anchoring of the peptides to the MHC II molecules occurs by means of hydrogen bonds between the backbone of the peptide and the amino acids of the groove and by means of residues accommodated by pockets for specificity. Five pockets, called P1, P4, P6, P7 and P9, correspond to the amino acid of the peptide which it accommodates, the first position being that which is in the first pocket, receive amino acids of the peptide and are composed of conserved or polymorphic residues. The polymorphic residues are responsible for various specificities between MHC II molecules. Since the binding site is open, two peptides binding one MHC II molecule may do so according to different modes, that is to say using different anchoring residues in their sequence.

Brief Summary Text (45):
In order to be able to introduce residues which preserve or increase the binding activity, the modes of interaction of the peptides P81-93 and P85-97 with respect to the HLA-DR molecules capable of binding them were studied. The approach chosen was to introduce into each position an alanine so as to evaluate the role of the side chain in the interaction or a lysine which is a basic and bulky amino acid. If necessary, a combination of mutations was introduced. By way of example, a reduction in activity caused by substitutions of phenylalanine 88 by a lysine or an alanine is observed in FIG. 6. Other reductions in activity are observed a positions situated at 3, 5 and 8 amino acids from phenylalanine 88. This activity profile corresponds to a mode of binding where positions F88, I91 T93 and Y96 are accommodated by the pockets P1, P4, P6 and P9, respectively, of the molecules HLA-DRB3*0101, HLA-DRB5*0101, HLA-DRB1*1301 and HLA-DRB1*0701. This mode of association was confirmed by molecular modeling for the complexes: P85-97/DRB3*0101, P85-97/DRB5*0101 and P81-93/DRB4*0101. All the results are given in FIG. 7. It is observed that on sequence 81-97, there are at least six modes of binding to the HLA-DR molecules. It is also observed that mode I is common to eight molecules whereas modes V and VI are specific to a single molecule.

Brief Summary Text (52):
The subject of the present invention is also desensitizing compositions for bee venom allergies, characterized in that they comprise: at least one peptide selected from group A consisting of: the peptides of group I, as defined above, and the peptides consisting of fragments of at least 13 amino acids which are included in or comprise the fragment corresponding to positions P81-97 of the major bee venom allergen (API m1) and which bind at least to the HLA-DR molecules encoded by the HLA alleles DRB1*0101, DRB1*0301, DRB1*0401, DRB1*0701, DRB1*1101, DRB1*1301 and DRB1*1501 (molecules DR1, DR3, DR4, DR7, DR11, DR13 and DR2), with a binding activity <1000 nM, and at least one pharmaceutically acceptable vehicle.

Brief Summary Text (54):
According to an advantageous embodiment of said compositions, they preferably consist of a mixture of peptides comprising: at least one group A peptide as defined above and at least one other peptide selected from the following groups: the peptides selected from group B consisting of: the peptides of group II, as defined above, and the peptides consisting of fragments of at least 13 amino acids which are included in or comprise the fragment corresponding to positions 94-106 of the major bee venom allergen (API m1) and which bind at least to the HLA-DR molecules expressed by the alleles DRB1*0101, DRB1*0401 and DRB1*1101 (molecules DR1, DR4 and DR11), with a binding activity <1000 nM, the peptides selected from group C consisting of: the peptides of group III, as defined above, and the peptides consisting of fragments of at least 13 amino acids which are included in or comprise the fragment corresponding to positions P76-94 of the major bee venom allergen and which bind at least to the HLA-DR molecules expressed by the alleles DRB1*0701, DRB1*1101 and DRB1*1501 (molecules DR7, DR11 and DR2), with a binding activity <1000 nM, and the peptides selected from group D consisting of: the peptides of group IV, as defined above, and the peptides consisting of fragments of at least 13 amino acids which are included in or comprise the fragment corresponding to positions P122-134 of the major bee venom allergen and which bind at least to the HLA-DR molecules expressed by the alleles DRB1*1101, DRB1*1301 and DRB1*1501 (molecules

DR11, DR13 and DR2), with a binding activity <1000 nM.

Brief Summary Text (59):
These desensitizing compositions are defined from the activities for binding to the HLA-DR molecules of the peptides which they comprise, from the frequency of alleles toward which they are active and from the complementarity of the zones for interaction or epitopes which said peptides carry.

Brief Summary Text (63):
The peptides included in said compositions were advantageously selected using an HLA-DR/peptide binding test comprising (i) incubating the purified HLA-DR molecules selected from those relating to more than 5% of a given population and in particular the HLA molecules DR1, DR3, DR4, DR7, DR11, DR13 and DR2, simultaneously with various concentrations of fragments of 13 to 18 amino acids which overlap and which completely cover the API m1 sequence and with a reagent R1 consisting of a peptide fragment combined with a nonradioactive marker, such as biotin and whose sequence is different from said peptides and is chosen such that it exhibits affinity toward the chosen HLA-DR molecule, such that it can be used at a concentration <200 nM, (ii) transferring the complexes obtained on an ELISA-type plate, previously sensitized with an antibody specific for all the HLA-DR molecules, (iii) revealing the HLA-DR molecules/R1 reagent complexes, attached to the bottom of the plate by means of suitable conjugates, such as streptavidin-phosphatase and a fluorescent substrate, (iv) selecting the peptides comprising different epitopes, that is to say the most representative of the various zones of interaction between the major bee venom allergen and the HLA-DR molecules and (v) choosing the most suitable peptides as a function of the frequency of the alleles toward which they exhibit a binding activity <1000 nM, corresponding to the concentration of this peptide which inhibits 50% of the binding of the reagent R1 (IC.sub.50).

Brief Summary Text (64):
These tests make it possible, unambiguously, to combine with each allele of the 1st gene or of the 2nd gene, the sequences of the fragments capable of binding thereto or on the contrary which do not bind thereto.

Brief Summary Text (67):
Thus, the inventors have found that only some peptides have a binding activity with respect to several of the most frequent alleles in the Caucasian population in accordance with Tables IIIa and IIIb.

Brief Summary Text (71):
The peptides which can be included in a desensitizing composition for bee venom allergies may be advantageously selected by a method which comprises: (i) incubating the purified HLA-DR molecules selected from those relating either to less than 5% of a given population, that is to say those consisting of HLA-DRs other than the HLA molecules DR1, DR3, DR4, DR7, DR11, DR13 and DR2, or HLA-DR molecules from a given patient, simultaneously with various concentrations of fragments of 13 to 18 amino acids which overlap and which completely cover the API m1 sequence and with a reagent R1 consisting of a peptide fragment combined with a nonradioactive marker such as biotin and whose sequence is different from the peptides, as defined above (groups A to D) and is chosen so that it exhibits affinity toward the chosen HLA-DR molecule, such that it can be used at a concentration <200 nM, (ii) transferring the complexes obtained on a microtiter plate, previously sensitized with an antibody specific for all the HLA-DR molcules, (iii) revealing the HLA-DR molecules/R1 reagent complexes, attached to the bottom of the plate by means of suitable conjugates, such as streptavidin-phosphatase and a fluorescent substrate, (iv) selecting the peptides comprising different epitopes, that is to say the most representative of the various zones of interaction between the major bee venom allergen and the HLA-DR molecules studied and (v) choosing the most suitable peptides as a function of the frequency of the alleles toward which they exhibit a binding activity <1000 nM, corresponding to the concentration of this peptide which inhibits 50% of the binding of the reagent R1 (IC.sub.50).

Brief Summary Text (75):
To study the HLA-DR molecules (2nd gene), this requires appropriate pairs of biotinylated peptides which should bind the preparation at low concentration and be

selective for one of the two molecules. More precisely, the binding of the biotinylated peptides should be effectively inhibited by their nonbiotinylated homolog, but not greatly disrupted by the nonbiotinylated form of the other peptide (Table X). It has been possible to find such peptides for each of the molecules DRB3*0101, DRB4*0101 or DRB5*0101.

Drawing Description Text (2):
FIG. 1 represents the protein sequence of bee venom phospholipase A2 (API m1) (SEQ ID NO: 8), deduced from that of the complementary DNA,

Drawing Description Text (3):
FIG. 2 illustrates the activity for binding to the HLA-DR molecules of the peptides of thirteen amino acids which cover sequence 15-37 of the major bee venom allergen. The results are expressed in the 1/IC.sub.50 form. The unit is M.sup.-1 ;

Drawing Description Text (4):
FIG. 3 illustrates the activity for binding to the HLA-DR molecules of the peptides of thirteen amino acids which cover sequence 107-134 of the major bee venom allergen. The results are expressed in the 1/IC.sub.50 form. The unit is M.sup.-1 ;

Drawing Description Text (8):
FIG. 7 illustrates the modes of binding of the sequence 81-97 to the HLA-DR molecules. The blocks schematically represent the site of binding of the HLA-DR molecules which characterize the pockets P1, P4, P6, P7 and P9. A color and a number in Roman numeral was attributed to each mode so as to facilitate their visualization; and

Detailed Description Text (3):
Principle of the Binding Tests

Detailed Description Text (8):
The hybridomas secreting a monomorphic antibody specific for the HLA-DR molecules is in particular that described in Southwood et al. (52) or that described in Posch et al. (42). The antibodies are purified from culture supernatants on Protein A-Sepharose columns. These antibodies are coupled onto Sepharose 4B or Protein A-Sepharose columns for the purification of the HLA-DR molecules.

Detailed Description Text (9):
Tests for HLA-DR/Peptide Binding

Detailed Description Text (10):
The tests for binding of the peptides to the HLA-DR molecules are competition tests with immunoenzymatic visualization, initially developed by Hill on the HLA-DR molecule (37). They are carried out in 96-well plates, which makes it possible to study numerous samples in the same experiment. Briefly, the purified HLA-DR molecules are incubated with a biotinylated peptide which serves as tracer and various concentrations of the peptide to be tested.

Detailed Description Text (11):
After incubating for 24 to 72 hours, the samples are neutralized, and then 100 .mu.l of each sample are transferred onto an ELISA plate previously sensitized by the monomorphic antibody specific for the HLA-DR molecules. The HLA-DR molecules/biotinylated peptide complexes attached at the bottom of the plate via the monomorphic antibody specific for the HLA-DR molecules are visualized by means of the streptavidin-phosphatase conjugate and a fluorescent substrate. The activity of each peptide is characterized by the concentration of this peptide which inhibits the binding of the biotinylated peptide by 50% (IC.sub.50).

Detailed Description Text (12):
Choice and Optimization of the Binding Tests

Detailed Description Text (19):
The choice of the biotinylated peptides is the key element in the specificity of the test. Most of the cells used possess two different HLA-DR molecules which are both purified by a monomorphic antibody specific for the HLA-DR molecules and both are

recognized by the same antibody. In order to unambiguously study the binding of a peptide to the DRB1 allele, it is necessary to ensure that the biotinylated peptide binds this allele and does not bind the product of the other gene.

Detailed Description Text (21):
For HLA-DRB1*0101, DRB1*0401 and DRB1*1101, the peptide ha 306-318 which other authors had previously used in tests for binding to these alleles (37, 41), was used.

Detailed Description Text (27):
Activity for binding to the HLA-DR molecules of the peptides of eighteen amino acids which cover the sequence of the major bee venom allergen (SEQ ID NO: 8).

Detailed Description Text (33):
The peptides which are naturally present on the HLA-DR molecules have sizes which vary between 13 and 25 amino acids approximately, the size most frequently encountered being 15 amino acids. In order to optimize the search for the peptides of API m1 which are capable of binding to the HLA-DR molecules, we synthesized thirty peptides of 18 amino acids which overlap by 14 amino acids and which therefore contain all the peptides of 15 possible residues of the API m1 sequence. The binding capacities of each of these peptides were tested on the 7 alleles which we selected and are expressed in the IC.sub.50 form (Table VII).

Detailed Description Text (35):
Clearly, each allele possesses a profile for binding of the peptides of API m1 which is specific to it. Some peptides bind to only one allele (for example P105-122 to allele 401, P69-86 and P73-90 to allele 1301). Others, by contrast, bind to several alleles. That is the case in particular for peptide P81-98 which significantly binds the seven alleles studied and for peptide P85-102 which significantly binds six alleles. In many cases, a peptide is common to two or several alleles. These common peptides define mainly three distinct zones of the API m1 sequence: i) an N-terminal part which the peptides P13-30, P17-34, P21-38 form, ii) a central part consisting of the peptides P77-94 to P93-110 and iii) a C-terminal part which includes the peptides P113-122 to P117-134. It is also observed that thirteen peptides out of the thirty tested have binding activities >1000 nM, regardless of the MHC II molecule studied. They are therefore inactive or not very active.

Detailed Description Text (36):
Table VIII below illustrates the activity for binding to the HLA-DR molecules of the peptides of 13 amino acids which cover the zone 73-108 of API m1.

Detailed Description Text (37):
Activity for binding to the HLA-DR molecules of the peptides of 13 amino acids which cover the zone 73-108 of the major bee venom allergen (SEQ ID NO: 8).

Detailed Description Text (42):
11 peptides which exhaustively cover the N-terminal part 15 to 37 were tested on the alleles 101, 401, 701, 1101 and 1301 (FIG. 2). For the allele 701, the peptides P18-30 to P22-34 exhibit a significant binding activity which, in the case of the peptide P18-30, is equivalent to that of the peptide of eighteen amino acids P21-38.

Detailed Description Text (43):
The alleles 401, 101 and 1101 substantially bind the same peptides as the allele 701. However, the binding activities observed are lower, which is in agreement with those obtained for the peptides of eighteen amino acids.

Detailed Description Text (44):
The central part was studied on the seven alleles by means of twenty-four peptides of thirteen residues. For the allele 101, the peptides P85-97, on the one hand, and P91-103 to P95-107, on the other hand, define two distinct zones of interaction. These two zones are also found for the alleles 401 and 1101 but with small variations. The first comprises, in addition to the peptide P85-97, the peptides P82-94 and P83-95 for the allele 401 and the peptide P83-95 for the allele 1101. The second zone of contact is strictly identical between the allele 401 and 101 whereas

it is reduced to a single peptide (P94-106) for the allele 1101. The allele 701 is characterized by three peptides having good binding activity (P85-97, P86-98 and P87-99) which corresponds to that of the peptides of eighteen amino acids P81-98 and P85-102. The good activity for binding of the peptide P77-94 to the allele 701 previously described is not observed for any of the peptides of thirteen residues which cover this zone, the peptides P76-88 to P81-93 having a substantially lower activity.

Detailed Description Text (45):
The peptide P85-97 possesses, for the alleles 301 and 1301, a binding activity similar to that of the peptides of 18 amino acids P81-98 and P85-102, containing it. The allele 1301 also accepts the peptide P86-105 as ligand. For the allele 1501, seven peptides, including six which are consecutive (P73-85 to P78-90) and one which is isolated (P81-93) reflect the activity of the three peptides of eighteen amino acids (P73-90, P77-94 and P81-98)

Detailed Description Text (47):
These results describe the precise location of the binding determinants of the major bee venom allergen for the seven alleles chosen and clearly show the differences and the similarities between the alleles for the various peptides of API m1. In order to better account for the activity and the location of these determinants, a representative peptide, which is as short as possible and whose binding activity reflects that of the determinant (Table III) was chosen for each of them. It will be noted most particularly that the peptide P85-97 is representative of a determinant for the alleles 101, 401, 1101, 701, 301 and 1301 and that other determinants are advantageously situated near this peptide (P76-88, P77-94, P81-93, P94-106).

Detailed Description Text (49):
To evaluate the impact of the most active peptides (activity less than 1000 nM) within the Caucasian population, the cumulative frequency of the alleles which they are capable of binding (FIG. 4) was calculated for each. Applied to all the peptides of 18 amino acids which completely cover the sequence of the major allergen, this representation makes it possible to weight the activity of the peptides tested. It is clearly observed that the central zone ranging from the peptide P77-94 to the peptide P93-110 is that which has the greatest impact in the population. The peptide P81-98 binding with a good affinity to all the HLA-DRs studied, covers on its own 63% of the population and combines the impact of the determinants carried by the peptides P85-97 and P81-93. The addition of sequences at the N- and C-terminals makes it possible to add to this combination of determinants other zones of interaction such as P76-88, P77-94 and P93-106 which relate to nonnegligible percentages of the population. Finally, the impact of the peptides P117-134 or 122-134 greater than 20% is observed at the C-terminal.

Detailed Description Text (52):
The peptides which bind to the HLA molecules are not necessarily stimulating for the T lymphocytes. They can indeed resemble self-peptides, such that no T lymphocyte will be capable of recognizing them. On the other hand, it has previously been shown that all the peptides which stimulate the T lymphocytes are part of the best peptides which bind to the MHC II molecules (60). The binding to the MHC II molecules is therefore a necessary but insufficient condition for allowing a peptide to be recognized by the T lymphocytes. In order to verify that the peptides which were identified are effectively capable of stimulating T lymphocytes in allergic patients, their stimulating capacity was tested (FIG. 8). The cells used are peripheral blood cells from people allergic to bee venom. These people came to the Rothschild Hospital to be desensitized and agreed to participate in this study (DGS No. 980457). Given the small number of cells, the peptides were grouped into different pools. The cells from one patient did not result in any proliferation (not shown). Of the six patients for whom reactivity was observed, a high variability was observed in the intensity of the response to the peptides, in the nature and the number of active peptides. However, it is observed that of the 6 patients, 5 respond to pool 7 which comprises peptides which cover zone 77-111 and 3 respond to pool 9 which covers zone 105-134.

Detailed Description Paragraph Table (3):
TABLE VI Protein Tracer concen- concen- Incubation tration tration Optimum time

Alleles (.mu.g/ml) Tracers (nM) pH (h) DRB1*0101 0.6 HA 306-318 10 6 24 DRB1*0301 2.3 MT 2-016 50 4.5 72 DRB1*0401 1.6 HA 306-318 30 6 24 DRB1*0701 0.4 YKL 10 5 24 DRB1*1101 1.3 HA 306-318 20 5 24 DRB1*1301 0.7 B1 21-36 200 4.5 72 DRB1*1501 0.5 A3 152-166 10 4.5 24

Detailed Description Paragraph Table (6):
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Other Reference Publication (1):
Dierdre O'Sullivan et al., "Characterization of the Specificity of Peptide Binding To Four DR Haplotypes", J. Immunol., 1990, vol. 145, No. 6, pp. 1799-1808.

Other Reference Publication (6):
Alexander Faith et al., "An Altered Peptide Ligand Specifically Inhibits Th2 Cytokine Synthesis by Abrogating TCR Signaling",J. Immunol., vol. 162, No. 3, Feb. 1, 1999, pp. 1836-1842.

CLAIMS:

1. A polypeptide molecule capable of desensitizing a human subject to bee venom, the polypeptide selected from the group consisting of: (a) a polypeptide molecule corresponding to amino acid positions 85-97 of SEQ ID NO: 8; (b) a polypeptide molecule corresponding to amino acid positions 81-93 of SEQ ID NO: 8; (c) a polypeptide molecule corresponding to amino acid positions 94-106 of SEQ ID NO: 8; (d) a polypeptide molecule corresponding to amino acid positions 76-88 of SEQ ID NO: 8; (e) a polypeptide molecule corresponding to amino acid positions 77-94 of SEQ ID NO: 8; (f) a polypeptide molecule corresponding to amino acid positions 122-134 of SEQ ID NO: 8; and (g) a polypeptide molecule of (a)-(f) comprising at least one amino acid substitution, wherein the substituted polypeptide exhibits binding activity to MHC class II molecules identical to or greater than that of the polypeptides (a)-(f).

5. A pharmaceutical composition for desensitizing a human subject to bee venom, the composition comprising: at least one polypeptide molecule corresponding to amino acid positions 85-97 of SEQ ID NO: 8 or to amino acid positions 81-93 of SEQ ID NO: 8; at least one polypeptide molecule of at least 13 amino acids and corresponding to a consecutive amino acid sequence within the range of amino acid positions 81-97 of SEQ ID NO: 8 and which binds to at least one HLA-DR molecule encoded by the HLA alleles DRB1*0101, DRB1*0301, DRB1*0401, DRB1*0701, DRB1*1101, DRB1*1301 or DRB1*1501 with a binding activity <1000 nM; and at least one pharmaceutically acceptable vehicle.

6. A pharmaceutical composition for desensitizing a human subject to bee venom comprising: (a) at least one polypeptide molecule corresponding to amino acid positions 85-97 of SEQ ID NO: 8 or to amino acid positions 81-93 of SEQ ID NO: 8; (b) at least one polypeptide molecule of at least 13 amino acids and corresponding to a consecutive amino acid sequence within the range of amino acid positions 81-97 of SEQ ID NO: 8 and which binds to at least one HLA-DR molecule encoded by the HLA alleles DRB1*0101, DRB1*0301, DRB1*0401, DRB1*0701, DRB1*1101, DRB1*1301 or DRB1*1501 with a binding activity <1000 nM; (c) at least one polypeptide molecule corresponding to amino acid positions 94-106 of SEQ ID NO: 8 or a polymer thereof; (d) at least one polypeptide molecule of at least 13 amino acids and corresponding to a consecutive amino acid sequence within the range of amino acid positions 94-106 of SEQ ID NO: 8, the molecule binding to at least one HLA-DR molecule encoded by the alleles DRB1*0101, DRB1*0401 or DRB1*1101 with a binding activity <1000 nM; (e) at least one polypeptide molecule corresponding to amino acid positions 76-88 or 77-94 of SEQ ID NO: 8 or a polymer thereof; (f) at least one polypeptide molecule of at least 13 amino acids and corresponding to a consecutive amino acid sequence within the range of amino acid positions 76-94 of SEQ ID NO: 8, the molecule binding to at least one HLA-DR molecule encoded by the alleles DRB1*0701, DRB1*1101 or DRB1*1501 with a binding activity <1000 nM; (g) at least one polypeptide molecule corresponding to amino acid positions 122-134 of SEQ ID NO: 8 or a polymer thereof; (h) at least one polypeptide molecule of at least 13 amino acids and corresponding to a consecutive amino acid sequence within the range of amino acid positions 122-134 of SEQ ID NO: 8, the molecule binding to at least one HLA-DR molecule encoded by the alleles DRB1*1101, DRB1*1301 or DRB1*1501 with a binding activity <1000 nM; and (i) at least one pharmaceutically acceptable vehicle, wherein any polypeptide may contain at least one mutation such that the resultant mutant binds at least to one HLA-DR molecule encoded by the alleles DRB1*0101, DRB1*0301, DRB1*0401, DRB1*0701, DRB1*1101, DRB1*1301 or DRB1*1501 with a binding activity <1000 nM.